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Tetrahedron Letters 48 (2007) 5039–5042
Tetrahedron Letters

2-Oxobenzo[*h*]chromene: a novel entry for the synthesis of functionalized angular polycyclic azaarenes☆

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Received 22 March 2007; revised 7 May 2007; accepted 17 May 2007
Available online 24 May 2007

Abstract—An efficient and short synthesis of (5,6-dihydrobenzo[*h*]pyrido[2,1-*b*]quinazolin-2-ylidene)acetonitriles, (5,6-dihydrobenzo[*h*]pyrazino[2,1-*b*]quinazolin-2-ylidene)acetonitriles and (5,6-dihydrobenzimidazo[1,2-*b*]benzo[*f*]isoquinolin-7-yl)acetonitriles in good yields is delineated through base catalyzed ring transformation of 4-(piperidin-1-yl)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles with 2-amino-pyridine, 2-aminopyrazine and (imidazo-2-yl)acetonitrile.

Introduction of nitrogen atoms into polycyclic arenes, increases their polarity as well as improves their solubility and bioavailability.[1] These polycyclic azaheteroaromatics are environmental pollutants, formed and released into the atmosphere from various anthropogenic sources, such as incomplete combustion of fossil fuels, industrial effluents, oil spills and drilling, refining, and coal-tar distillation. Some of these are products of amino acid pyrolysis during broiling, frying and baking.[2,3] These polycyclic azaarenes show mutagenic and toxic effects as a result of a metabolic activation. The planarity and electrophilic nature of the azaarenes cause the genotoxicity.[4]

The benzoquinazoline ring system is present as a substructure in various natural product alkaloids of therapeutic importance such as rutecarpine[5] (**I**) and ardeemin[6] (**II**). Benzimidazo[2,1-*b*]benzo[*f*]isoquinoline (**III**) ring system[7] is present in pharmacologically active compounds. These polyazaarenes display pronounced biological activities[8–11] as anticancer, diuretic, anticonvulsant and antihypertensive agents (Fig. 1).

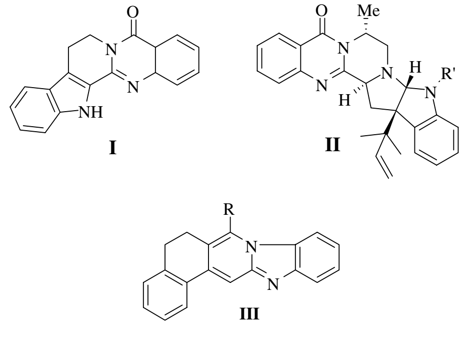

Figure 1. Rutecarpine (**I**), ardeemin (**II**) and benzimidazo[2,1-*b*]benzo[*f*]isoquinoline (**III**).

A comprehensive literature survey revealed that the chemistry of benzo[*h*]pyrido[2,1-*b*]quinazolines (**6**) and benzo[*h*]pyrazino[2,1-*b*]quinazolines (**8**) has not been explored extensively. Recently, benzo[*h*]pyrido[2,1-*b*]quinazolines have been synthesized[12] from the reaction of ethyl 4-aryl-6-trichloromethylpyridine-3-carboxylates with anthranilonitrile. Alternatively, they have also been obtained[13] from the base catalyzed reaction of pyridoquinazoline and chloroacetonitrile in DMF.

Compounds with the pyrazino[2,1-*b*]quinazoline ring skeleton have been prepared by the reaction of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates with ethylenediamine.[14] There is only one example of a similar heterocyclic system, reported in the literature[15] from the reaction of isatoic anhydride via a 2-chloroformyl-4*H*-3,1-benzoxazin-4-one.

5,6-Dihydrobenzimidazo[1,2-*b*]benzo[*f*]isoquinolines were synthesized earlier by the condensation–cyclization[7] of oxoketene dithioacetals derived from 1-tetralone and 2-methyl/cyanomethylbenzimidazole. This approach

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Keywords: 2-Oxobenzo[*h*]chromenes; Ring transformation; Quinazoline; Benzo[*f*]isoquinoline.

☆ CDRI Communication No. 7216.

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0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.106

has synthetic limitations including obtaining only the 7-methylsulfanyl substituted derivative, and using pyrophoric reagents.

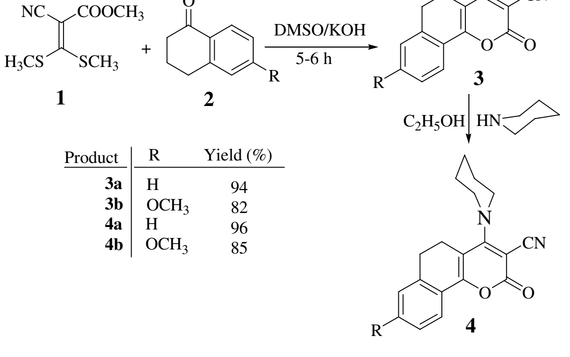
Herein, we report a very simple, economical and versatile protocol for the construction of benzo[*h*]pyrido[2,1-*b*]quinazolines, benzo[*h*]pyrazino[2,1-*b*]quinazolines and benzimidazo[1,2-*b*]benzo[*f*]isoquinolines through base catalyzed ring transformation of 4-(piperidin-1-yl)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles (**4**) using 2-aminopyridine (**5**), 2-aminopyrazine (**7**) or (benzimidazol-2-yl)acetonitrile (**9**) as nucleophiles.

4-(Piperidin-1-yl)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles (**4**) as starting materials were prepared by reaction of methyl 2-cyano-3,3-dimethylthioacrylate (**1**) with 1-tetralone (**2**) in the presence of powdered KOH in DMSO followed by amination of the intermediate 2-oxo-4-methylsulfanyl-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles (**3**) with piperidine in refluxing ethanol as described earlier (Scheme 1).[16]

As is evident from the topography of 4-*sec*-amino-2-oxo-5,6-dihydrobenzo[*h*]chromene-3-carbonitriles (**4**), they possess three electrophilic centres C-2, C-4 and C-10b in which the latter is highly prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at position 3 of the chromene ring.

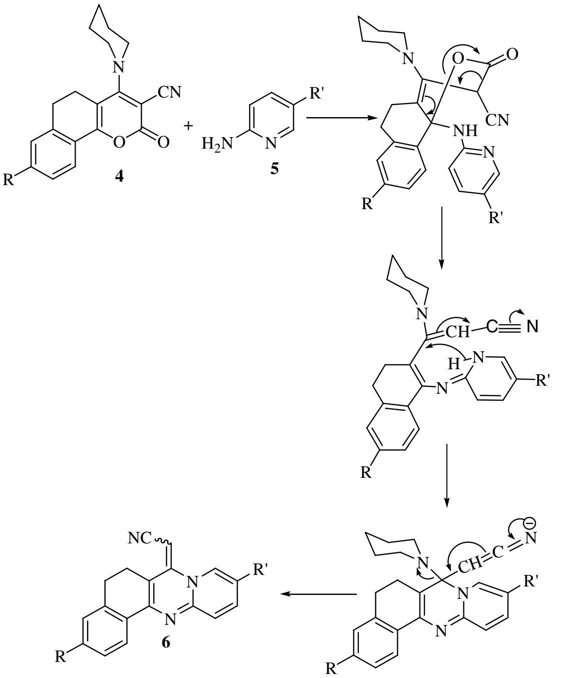
Thus, stirring an equimolar mixture of **4** and 2-aminopyridine in DMF in the presence of powdered KOH at room temperature for 2–3 h followed by work-up led to (5,6-dihydrobenzo[*h*]pyrido[2,1-*b*]quinazolin-2-ylidene)acetonitriles (**6**) in good yields. The reaction is possibly initiated through attack of the amino group of **5** at C-10b with ring opening and loss of carbon dioxide followed by ring closure involving C-4 and the ring nitrogen of pyridine to give **6** as a mixture of (*E*)- (minor, ~30%) and (*Z*)- (major, ~70%) isomers (Scheme 2).

Under analogous conditions, reaction of **4** with 2-aminopyrazine **7** using powdered KOH as a base and DMF as solvent gave (5,6-dihydrobenzo[*h*]pyrazino[2,1-*b*]quinazolin-2-ylidene)acetonitriles (**8**) in very

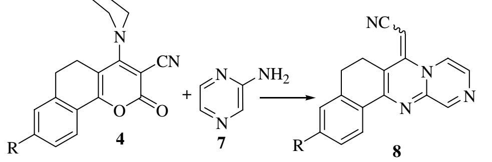


Product	R	Yield (%)
3a	H	94
3b	OCH_3	82
4a	H	96
4b	OCH_3	85

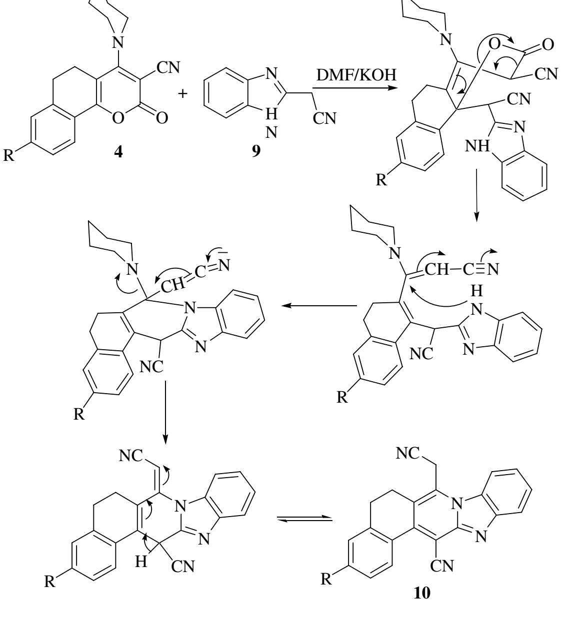
Scheme 1. Synthesis of 5,6-dihydro-4-*sec*-amino-2-oxo-2*H*benzo[*h*]-chromenes (**4**).



Scheme 2. Mechanism involved in the synthesis of (5,6- dihydrobenzo[*h*]pyrido[2,1-*b*]quinazolin-2-ylidene)acetonitriles (**6**).



Scheme 3. Synthesis of (5,6-dihydrobenzo[*h*]pyrazino[2,1-*b*]quinazolin-2-ylidene)acetonitriles (**8**).



Scheme 4. Mechanism involved in the synthesis of (5,6-dihydrobenzimidazo[1,2-*b*]benzo[*f*]isoquinolin-7-yl)acetonitriles (**10**).