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# Guanidine and amidine mediated synthesis of bridgehead triazaphenalenes, pyrimidines and pyridines through domino reactions☆

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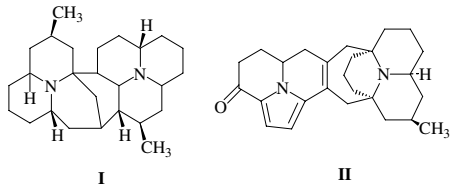
**Abstract**—An efficient and concise synthesis of 8-amino-2,5-diaryl-1,9,9b-triazaphenalene-4-carbonitriles has been delineated through two successive base catalyzed heteroaromatic annulations of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles by guanidine hydrochloride in moderate yield. This reaction was further explored through the ring transformation of **4** with amidines **8** and **11** to afford (2,6-diarylpyrimidin-4-yl)acetonitriles and 6-aryl-4-(piperidine-1-yl)nicotinonitriles in excellent yields.


The bridgehead azaphenalene ring system is a substructure of various natural products. Recently, isopsyllorine A **I**,[1] a new dimeric azaphenalene, and chilocorine[2] **II**, (Fig. 1) a heptacyclic alkaloid were isolated from the ladybird beetles, *Halyzia 16-guttata* and *Vibdia 12-guttata*. Some of these compounds are useful as antimicrobial agents[3,4] and are effective against a variety of multidrug resistant bacteria.

1,9,9b-Triazaphenalene is a tricyclic molecule, possessing a completely conjugated perimeter of $sp^2$-hybridized carbon and nitrogen atoms, with a centrally located $sp^3$-hybridized nitrogen.



**I** **II**

**Figure 1.**

*Keywords*: 2-Oxo-4-(piperidin-1-yl)-5,6-dihydro-2*H*-benzo[*h*]-chromene-3-carbonitriles; Oxaheteroaromatics; Ring transformation.
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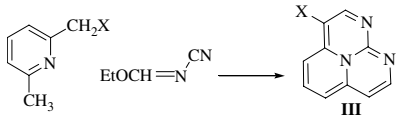
An extensive literature survey revealed that unsubstituted 1,9,9b-triazaphenalene was first synthesized by Ceder et al.[5] in 1976 from the reaction of 2,6-dimethylpyridine or (6-methylpyridin-2-yl)acetonitrile or (6-methylpyridin-2-yl)acetate with ethoxymethylenecyanamide separately in very low yield (see Scheme 1).

The pyrimidine ring is an integral part of various natural products[6] and serves as a building block for various pharmaceuticals and biopolymers. It also has very good coordinating ability similar to pyridyl ligands in supramolecular metallogrid-like architecture.[7] In addition, pyrimidines are pharmacologically active and display anticonvulsant,[8] antiinflammatory,[9] antibacterial[10] and antimycotic[11] activities.

A common approach for the construction of a pyrimidine ring is through condensation of 1,3-dicarbonyl compounds with amidines.[12] However, 2,4,6-triarylpyr-



**III**
X = H, CN, COOEt

**Scheme 1.** Ceder's procedure for the synthesis of 1,9,9b-triazaphenalene.

imidines are constructed stepwise.[12] The use of formamide or an orthoester in combination with ammonia[13] as a potential surrogate NCN reagent has been reported in the synthesis of pyrimidines. Tris-(formylamino)methanes,[14] 2-amino-2-formylmalonaldehyde[15] and 3-methyl-5-nitro-3*H*-pyrimidin-4-one[16] have also been used as 1,3-dicarbonyl equivalents in pyrimidine synthesis. A simple cyclocondensation–cyclization of amidine with chalcones is an alternative route for the synthesis of pyrimidines.[17]

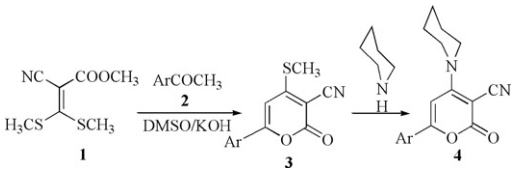
The utility of pyridine rings in understanding the chemistry of biological system has been realized greatly because of their presence as substructures in many natural products[18] and pharmacologically active molecules[19] with wide synthetic potential for generating molecular diversity of therapeutic importance, and the ability to catalyze both biological and chemical reactions.[18–22] 4-Dimethylaminopyridine (DMAP), is a highly demanding reagent, used as a catalyst in acylation reactions and also for activation of carboxylic acids without racemization of α-chiral centres.[22] Pyridines are excellent ligands for complexation with transition metals.[20b] Alkene pendant pyridine polymers are industrially useful as acid scavengers[20b] and as materials for chemical separations.

A very common approach for the synthesis of pyridines[23] involves condensation of a 1,5-diketone with ammonia followed by nitric acid oxidation. 2-Acetylfuran has also been used as a 1,5-dicarbonyl equivalent for the preparation of congested pyridines. The reaction of 1,3-dicarbonyl compounds and 3-aminoenones or nitriles is an alternative versatile approach for the construction of unsymmetrically substituted pyridines.[18] 2*H*-Pyran-2-ones have been used as a diene equivalent for the preparation[24] of congested ethyl nicotinates on reaction with aryl nitriles under Diels–Alder conditions. The synthesis of trisubstituted pyridines has been reported[25,26] from the reaction of deoxybenzoin, vinamidium species and ammonia in good yields as Cox-2 inhibitors.

The lack of a suitable synthetic route[4] for the construction of 1,9,9b-triazaphenalenes, pyrimidines and pyridines has necessitated the development of an innovative and efficient procedure for their construction in high yields.

Herein, we report a convenient and concise first synthesis of 8-amino-2,5-diaryl-1,9,9b-triazaphenalene-4-carbonitriles **6** through two successive base catalyzed ring transformations of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **4** with guanidine hydrochloride. Under analogous conditions, reaction of **4** with aryl amidines produced pyrimidines **9** in >85% yields while reaction with formamidine gave 3,4,6-trisubstituted pyridines **12** in excellent yields.

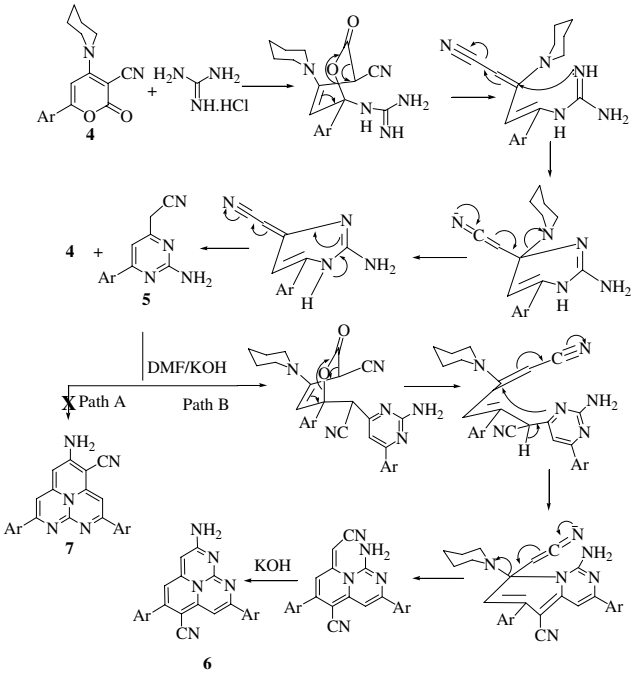
The precursor 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **4** were conveniently prepared in two steps (Scheme 2). The first step involved is formation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **3** from the reaction of an aryl methyl ketone **2** with methyl 2-cyano-3,3-dimethylthioacrylate **1** as described earlier.[27] Amination of **3** with piperidine in refluxing ethanol gave 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles[28] **4**. Thus, a mixture of 6-aryl-4-(piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **4**, guanidine hydrochloride and powdered KOH in DMF was stirred for 3–4 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% aqueous HCl (Scheme 3). The precipitate was filtered, washed with water and purified on neutral alumina column as a dark green solid, with very poor solubility in most organic solvents (see Table 1).




**Scheme 2.** Synthesis of 2*H*-pyran-2-ones **4**.

Attempts were made to trap the intermediate **5** using different solvents and bases at different temperatures but without success possibly due to instantaneous participation of the intermediate in a second ring transformation to yield 8-amino-2,5-diaryl-1,9,9b-triazaphenalene-4-carbonitriles **6**.

As is evident from the topography of 2*H*-pyran-2-ones **4,** the C-2, C-4 and C-6 positions are electrophilic in nature in which the latter is highly susceptible to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing CN substituent at




**Scheme 3.** Plausible mechanism for the synthesis of azaphenalene **6**.

**Table 1.** Yields of the azaphenalenes **6**

| 4, 6 | Ar | Yield (%) |
|---|---|---|
| **a** | $-C_6H_5$ | 54 |
| **b** | 4-Cl–$C_6H_4$ | 61 |
| **c** | 4-Br–$C_6H_4$ | 58 |
| **d** | 4-$CH_3$–$C_6H_4$ | 65 |
| **e** | 4-$CH_3O$–$C_6H_4$ | 55 |
| **f** | 2-Thienyl | 67 |
| **g** | 2-Naphthyl | 57 |
| **h** | 3,4-$CH_2O_2$–$C_6H_3$ | 61 |
| **i** | 3,4-$(Cl)_2$–$C_6H_3$ | 51 |

position 3 of the pyran ring. The base catalyzed reaction of **4** with guanidine hydrochloride is possibly initiated by attack of the $NH_2$ function at C-6 of the pyran ring with ring closure and loss of carbon dioxide and piperidine to form (2-amino-6-arylpyrimidin-4-yl)acetonitrile **5** as an intermediate, which in situ acts as a nucleophile for the subsequent ring transformation of **4**. The presence of two nucleophilic groups, $NH_2$ and $CH_2CN$ in intermediate **5** could result in the formation of **6** through path B or **7** through path A. However, ring transformation of **4** by a carbanion, generated in situ from the intermediate **5** provided **6** and not 5-amino-2,8-diaryl-1,9,9b-triazaphenalene-3-carbonitrile **7** (Scheme 3) through the participation of the amino group as a nucleophile. The mechanism of the reaction was further supported by the isolation and subsequent characterization of **6** through $^1H$ and $^{13}C$ NMR spectroscopy.

Of the two expected structures **6f** and **7f** (Fig. 2), the latter was discarded on the basis of the long-range HMBC spectra. From the $^1H$, $^{13}C$ and heteronuclear single quantum coherence (HSQC) spectrum of **6f**, the position of all the methine protons and carbons were elucidated. The HMBC spectrum showed three bond cross peaks between methine protons H-17 and H-18 and quaternary carbon C-15. Moreover, both of these protons (H17,18) demonstrated long range correlations with the thiophene rings, which would not be possible in structure **7f** in which only one methine proton could give a long range correlation with both the quaternary carbons (C-15) and thiophene ring. The other ring methine proton (H-11) showed two bond cross peaks with quaternary carbons (C-10 and C-12) and one three bond cross peak with the methine carbon (C-17), which, further corroborated the structure **6f**.

The NMR, IR and mass spectra of the isolated compounds supported the proposed structure. Compounds

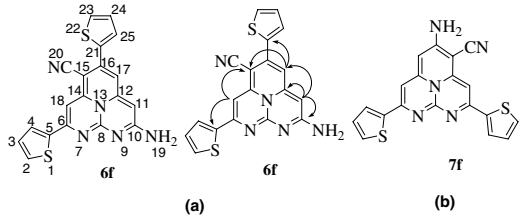
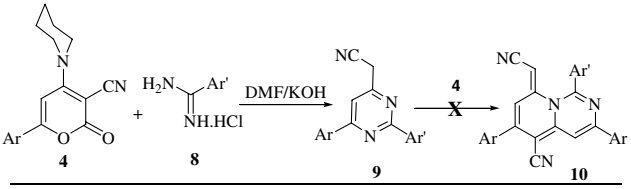



**Figure 2.** (a) Structure, numbering and selected HMBC correlations observed for compound **6f**; (b) structure of the other possible product **7f**.




| 9 | Ar | Ar' | Yields (%) |
|---|---|---|---|
| **a** | $C_6H_5$ | $C_6H_5$ | 85 |
| **b** | $C_6H_5$ | $C_6H_4N$ | 88 |

**Scheme 4.** Synthesis of (2,6-diarylpyrimidin-4-yl)acetonitriles **9**.

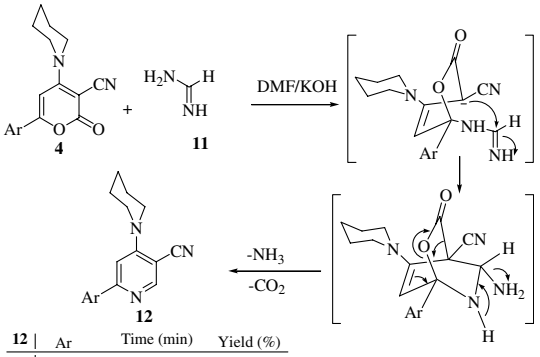
**6** were highly soluble in formic acid and TFA but were unstable.

Under analogous conditions reaction of **4** with arylamidine **8** gave (2,6-diarylpyrimidin-4-yl)acetonitriles[29] **9**, which did not participate further in ring transformation to form a product such as **10**, Scheme 4. From this reaction it was inferred that the contribution of the amino group is significant in successive ring transformations possibly due to the positive inductive effect, which increases the nucleophilicity of the molecule.

It was interesting to note that under similar conditions reaction of **4** with formamidine acetate **11** provided pyridine **12** following a different reaction path as depicted in Scheme 5. The initial step in this reaction is attack of the nitrogen nucleophile at C-6 of the 2*H*-pyran-2-one with ring closure followed by elimination of carbon dioxide and ammonia to give 6-aryl-4-*sec*-aminonicotinonitriles **12**. From this reaction, it was concluded that the presence of different substituents on the amidine carbon was the deciding factor for the formation of different products. The preference for the formation of **12** could be due to the lack of a lone pair of electrons or $\pi$-electron contribution of the amino or aryl group, which makes the formamidine carbon electrophilic and thereby facilitates intramolecular nucleophilic attack.

All the compounds synthesized were characterized by spectroscopic analysis.[30]

In conclusion, we have developed an efficient substituent dictated synthesis of 8-amino-2,5-daryl-1,9,9b-triaza-




| 12 | Ar | Time (min) | Yield (%) |
|---|---|---|---|
| **a** | $C_6H_5$ | 50 | 95 |
| **b** | 4-Cl.$C_6H_4$ | 60 | 93 |
| **c** | 4-$CH_3$.$C_6H_4$ | 50 | 98 |

**Scheme 5.** A plausible mechanism for the synthesis of pyridines **12**.

phenalene-4-carbonitriles, (2,6-diarylpyrimidin-4-yl)acetonitriles and 6-aryl-4-(piperidin-1-yl)nicotinonitriles in very good yields under mild reaction conditions using inexpensive reagents. The new protocols represent efficient and economical routes for the synthesis of azaheteroaromatics.

## Acknowledgement

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30. *Synthesis of 8-amino-2,5-di(4-methoxyphenyl)-1,9,9b-triaza-phenalene-4-carbonitrile* (**6e**): A mixture of 6-(4-methoxyphenyl)-4-piperidin-1-yl-2-yl-2*H*-pyran-2-one-3-carbonitrile **4e** (310 mg, 1 mmol) and guanidine hydrochloride (143 mg, 1.5 mmol), powdered KOH (112 mg, 2 mmol) in DMF (5 mL) was stirred for 3 h at room temperature. Excess DMF was removed under reduced pressure and the residue poured onto crushed ice with vigorous stirring. The aqueous solution was neutralized with 10% HCl (5 mL) and the precipitate obtained was filtered, and purified on a neutral alumina column, using 40% methanol in ethyl acetate as eluent. The product was isolated as a dark green solid; yield: 55%; mp >250 °C; IR (KBr): 2213 $cm^{-1}$; $^1H$ NMR: (300 MHz, DMSO-$d_6$): $\delta$ 3.97 (s, 3H, $OCH_3$), 3.99 (s, 3H, $OCH_3$), 5.03 (s, 1H, CH), 5.55 (s, 1H, CH), 6.04 (s, 1H, CH), 6.97 (d, $J = 7.8$ Hz, 2H, ArH), 7.14 (br s, 2H, $NH_2$), 7.39 (d, $J = 7.8$ Hz, 2H, ArH), 7.66–7.83 (m, 4H, ArH); MS *m/z* 422 ($M^+$+1); Anal. Calcd for $C_{25}H_{19}N_5O_2$ (421.15): C, 71.25; H, 4.54; N, 16.62. Found C, 71.35; H, 4.59; N, 16.56.
*General procedure for the synthesis of 6-aryl-4-sec-aminonicotinonitriles* (**12a**–**c**): These were obtained by stirring a mixture of 6-aryl-4-(*piperidin-1-yl*)-2*H*-pyran-2-one-3-car-

bonitrile **4** (1 mmol) and formamidine acetate **11** (1.5 mmol) in the presence of KOH (2 mmol) in dry DMF. The reaction mixture was poured onto crushed ice with vigorous stirring and the precipitate obtained filtered, washed with water, dried and purified by column chromatography using 30% hexane in chloroform as eluent. (**12a**) White powder; yield: 95%; mp 102–104 °C; IR (KBr): 2936, 2836, 2363, 2210, 1588, 1524, 1443, 1416, 1381, 1284, 1231, 1159, 1123, 1072, 1024, 984, 873, 782, 748 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.72–1.79 (m, 6H, $CH_2$), 3.57 (t, $J = 5.1$ Hz, 4H, $CH_2NCH_2$), 7.10 (s, 1H, ArH), 7.43–7.50 (m, 3H, ArH), 7.91–7.94 (m, 2H, ArH), 8.61 (s, 1H, ArH); MS *m*/*z* 264 ($M^+$+1); HRMS: (EI, 70 eV) calcd for $C_{17}H_{17}N_3$ 263.14225 ($M^+$) found for *m*/*z* 263.14210.