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SYNTHESIS OF THE NEW HETEROCYCLIC SYSTEM 5,6,10b-TRIAZAACEPHENANTHRYLENE, A NITROGEN ANALOGUE OF ARISTOLACTAMS

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Abstract – We describe the two-step sequence for transforming enaminothioenone **1** to the planar semicyclic amidine **2** *via* an ylidenemalononitrile enamine intermediate, leading to the formation of the new π-conjugated heterocyclic system 5,6,10b-triazaacephenanthrylene, structurally related to the naturally occurring alkaloid aristolactams.

Highly fused nitrogen-containing heterocyclic aromatic systems form an important group of bioactive naturally occurring alkaloids. Among many biologically attractive heterocyclic compounds containing dibenzo[*cd*,*f*]indol-4(5*H*)-one skeleton are aristolactam[1,2] derivatives that possess anticancer,[3,4] antimicrobial, antiplatelet, and anti-inflammatory activities (Figure 1). Derivatives containing azaacephenanthrylene fused system have been isolated from Annonaceae, Piperaceae, and Menispermaceae family plants and they have been used as traditional herbal medicines in China.[2] The synthesis of aristolactam FI[5] and their analogue 4,5-dihydronaphtho[3,2,1-*cd*]indole[6] were based on the construction of the core phenanthrene ring system in one-pot Susuki-Miyaura coupling/aldol-type cascade reactions[5] or palladium-catalyzed tandem C-H activation.[6]

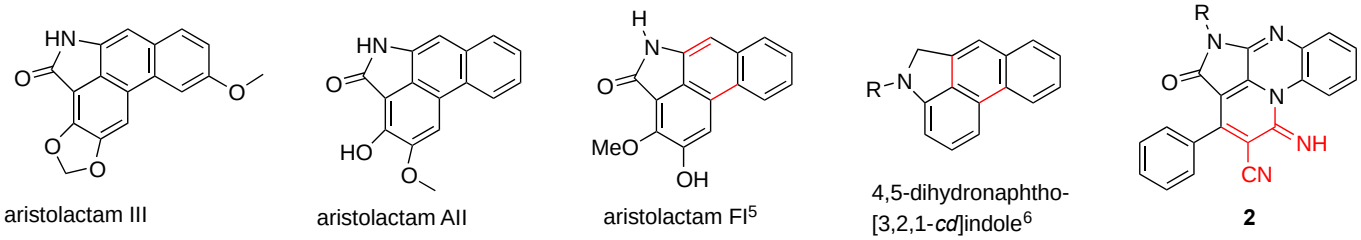
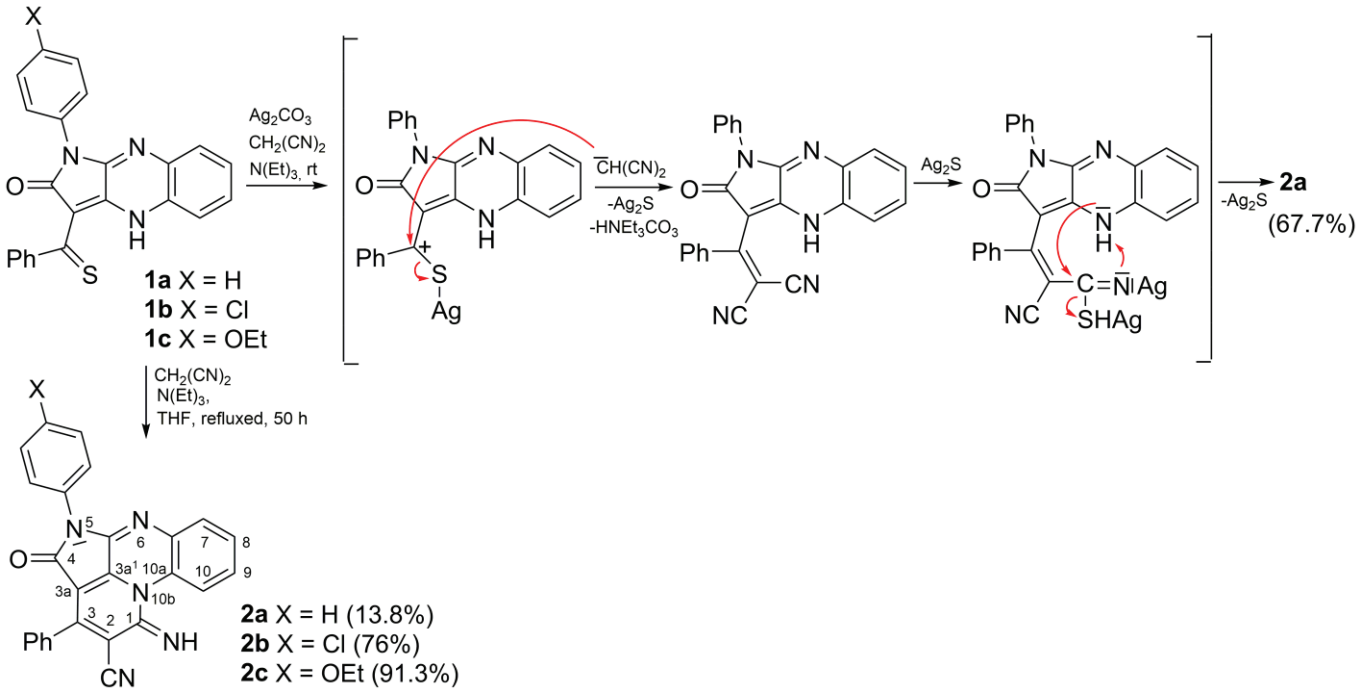


Figure 1. Structure of azaacephenanthrylene heterocyclic systems

As a continuation of our study on the synthesis of the fused pyrrolopyrazine[7-9] π-conjugated compounds

we report the synthesis of the new potentially bioactive 5,6,10b-triazaacephenanthrylene derivatives, structurally related to naturally occurring alkaloids aristolactams. These new heterocyclic system with three nitrogen atoms inbuilt to the acephenanthrylene framework is the first one described in the literature.

The synthesis was based on the construction of the core acephenanthrylene ring system in the two-step sequence for transforming enaminothioenone **1**[10] to the planar semicyclic amidine **2** *via* an ylidenemalononitrile enamine intermediate. Stable thioketones are versatile reagents that react efficiently with nucleophiles and electrophiles in thiophilic or carbophilic addition reactions.[11-13] These compounds readily undergo desulfurization in condensation with amines[10,14] and active methylene compounds in thio-Knoevenagel reactions[15] leading to imines and olefins. The thio-Wittig[16] or Barton-Kellogg[17,18] reactions can also be applied to thioketones in the formation of double carbon-carbon bonds with phosphonium ylide and diazo derivatives. These reactions are especially useful for the synthesis of highly sterically hindered olefins such as molecular motors[17] and π-type materials used in organic electronics.[18]



Scheme 1. Synthesis of **2**. Mechanism of silver ion-mediated formation of **2a**

The one-pot synthesis of 5,6,10b-triazaacephenanthrylene **2** was based on a two-step procedure: the thio-Knoevenagel condensation of enaminothioenone **1** with malononitrile and internal cyclization of ylidenemalononitrile enamine. The reaction proceeds under basic conditions with NEt_3 in boiling THF during 50 h. Products **2a-c** were purified by column chromatography using silica gel as the adsorbent and dichloromethane as the eluent. We obtained good yields for **2b** (76%) and **2c** (91.3%). However, the yield

for **2a** (13.8%) diverged significantly from the standard value. We modified the synthetic procedure using desulfurization by adding silver carbonate and conducting the reaction at rt for 24 h and we obtained **2a** with 67.7% yield. Silver ions[14,19] catalyze the cleavage of the carbon-sulfur double bond and activate the thiocarbonyl carbon atom, enabling the nucleophilic attack of ylidenemalononitrile. The reaction proceeds with the elimination of silver sulfide, which activates the nitrile group in thio-Pinner's manner[20] (Scheme 1).

Elemental analysis, IR, and MS data for **2** confirmed that the condensation occurred at the thiocarbonyl carbon atom. The absorption bands of nitrile groups and signal for nitrile ^{13}C carbon atoms appeared at 2204 cm^{-1}, 115.9 ppm for **2a**; 2214 cm^{-1}, 115.8 ppm for **2b**; 2215 cm^{-1}, 116.0 ppm for **2c**, respectively. The presence bands and signals of only one CN group prove evidently cyclization process. This cyclization of ylidenemalononitrile enamine was additionally determined by IR and ^{1}H NMR data (Supporting Information) showing imine N-H stretching vibration and chemical shift for imine protons at 3322 cm^{-1}, 9.0 ppm for **2a**; 3299 cm^{-1}, 9.0 ppm for **2b**; and 3299 cm^{-1}, 8.95 ppm for **2c**, respectively. Analyses of the correlations from 2D NMR experiments involving ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBCGP, and ^{1}H-^{13}C HSQCETGP for **2c** were used to assign the chemical shifts for the new heterocyclic system (Table 1, Supporting Information).

Table 1. NMR Spectral data for **2c** [600 MHz, $CDCl_3$, δ (ppm)]

Atom	^{13}C	^{1}H	^{1}H-^{1}H COSY	^{1}H-^{13}C HMBCGP	^{1}H-^{13}C HSQCETGP
1	156.8	-	-	-	=NH
2	133.8	-	-	-	=NH
3	103.8	-	-	-	=NH
3a	98.1	-	-	-	-
3a[1]	152.3	-	-	-	=NH
4	162.9	-	-	-	-
5a	148.8	-	-	-	-
6a	138.5	-	-	-	-
7	129.6	7.95	H-7/H-8	C-7/H-7	H-7/(C-10a; C-8,9; C-6a)
8	128.3	7.65	H-7/H-8; H-8/H-9	C-8/H-8	H-8/C-10
9	128.3	7.63	H-8/H-9; H-9/H-10	C-9/H-9	H-9/C-6a
10	121.8	10.35	H-9/H-10	C-10/H-10	H-10/(C-8,9; C-6a)
10a	127.1	-	-	-	-
31	130.7	-	-	-	-
32,36	129.1	7.68	-	C-32,36/H-32,36	-
33,35	128.4	7.54	-	C-33,35/H-33,35	-
34	131.3	7.55	-	C-34/H-34	-
51	124.3	-	-	-	-
52,56	127.9	7.46	H-52,56/H-53,55	C-52,56/H-52,56	-
53,55	115.0	7.01	H-52,56/H-53,55	-	-
54	158.6	-	-	-	-
OCH_2	63.8	4.08	H-CH_3/H-OCH_2	C-CH_2/H-CH_2	-
CH_3	14.8	1.44	H-CH_3/H-OCH_2	C-CH_3/H-CH_3	-
CN	116.0	-	-	-	-
=NH	-	8.95	-	-	=NH/(C-3; CN; C-2; C-3a[1]; C-1)

In summary, we have developed the application of thioketones as valuable starting materials in tandem thio-Knoevenagel condensation and cyclization in the synthesis of the new heterocyclic system 5,6,10b-triazaacephenanthrylene. This methodology is attractive not only as a new example of silver-mediated desulfurization but also as a simple and facile synthesis of a π-conjugated functional material. Synthesis of potentially bioactive structural analogues of aristolactams could open the new perspective for drug discovery.

EXPERIMENTAL

Melting points were determined on a *Boetius* PHMK 05 melting point apparatus. IR spectra were measured on a Thermo Scientific Nicolet IR 200 FT-IR. The ^{1}H NMR and ^{13}C NMR spectra were recorded using Brucker Avance III 600 and 300 spectrometers at 300 K. The chemical shifts (δ) are reported in parts per million (ppm) on a δ scale downfield from TMS. The ^{1}H NMR spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm). The ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.0 ppm). The coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded on a Finigan Mat 95 (EI 70 eV) and ESI spectrometers. Microanalyses were performed with a Vario Micro Tube CHNS.

General procedure for the synthesis of 1H-5,6,10b-triazaacephenanthrylene derivative:

Procedure A without Ag_2CO_3: 1-Phenyl-1,4-dihydro-2*H*-3-thiobenzoylpyrrolo[2,3-*b*]quinoxalin-2-one **1a** (0.79 mmol) was added to malononitrile (2.6 mmol) in THF (50 mL) with NEt_3 (2.25 mL). The reaction mixture was refluxed for 50 h. THF was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/CH_2Cl_2). Yield: (0.045 g, 13.8%).

Procedure B with Ag_2CO_3: 1-Phenyl-1,4-dihydro-2*H*-3-thiobenzoylpyrrolo[2,3-*b*]quinoxalin-2-one **1a** (0.3 g, 0.79 mmol) was added to malononitrile (0.2 g, 2.6 mmol) in THF (50 mL) with NEt_3 (2.25 mL) and Ag_2CO_3 (0.163 g, 0.59 mmol). The reaction mixture was stirred at rt for 24 h. THF was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel/CH_2Cl_2).

Synthesis of 1-imino-4-oxo-3,5-diphenyl-4,5-dihydro-1H-5,6,10b-triazaacephenanthrylene-2-carbonitrile (**2a**). Procedure B; Yield: (0.22 g, 67.7%), mp 283 °C. IR: 3322, 3116, 3029, 2204, 1717, 1646, 1600, 1579 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ 10.38-10.35 (m, 1H, H-10), 8.97 (s, 1H, NH), 7.98-7.95 (m, 1H, H-7), 7.71-7.4253 (m, 12H, Ar-H). ^{13}C NMR (75.47 MHz, $CDCl_3$), δ 162.6, 156.8, 152.3, 148.5, 138.3, 131.3, 130.7, 129.6, 129.1, 129.0, 128.50, 128.52, 128.4, 128.5, 128.0, 126.4, 121.8, 121.8, 115.9, 103.9, 98.1. MS-ESI: *m/z* 414 (M^++1). Anal. Calcd for $C_{26}H_{15}N_5O$: C, 75.53; H, 3.66; N, 16.94. Found: C,

75.24; H, 3.70; N, 16.89.

1-Imino-4-oxo-5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-5,6,10b-triazaacephenan-thrylene-2-carbo-nitrile (**2b**). Procedure A; Yield: (0.27 g, 76%), mp 310 °C. IR: 3299, 3132, 3058, 2214, 1722, 1645, 1619, 1578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 10.38-10.35 (m, 1H, H-10), 9.0 (s, 1H, NH), 7.98-7.95 (m, 1H, H-7), 7.69-7.48 (m, 11H, Ar-H). ^{13}C NMR (75.47 MHz, $CDCl_3$), δ 162.3, 156.7, 152.2, 148.2, 138.2, 133.8, 133.7, 131.3, 130.7, 129.6, 129.3, 129.00, 128.7, 128.5, 127.5, 127.1, 121.9, 115.80, 111.7, 104.2, 98.0. MS-ESI: *m/z* 448 (M^++1), 450 (M^++3). Anal. Calcd for $C_{26}H_{14}ClN_5O$: C, 69.72; H, 3.15; N, 15.64. Found: C, 69.49; H, 3.34; N, 15.62.

1-Imino-4-oxo-5-(4-etoxyphenyl)-3-phenyl-4,5-dihydro-1H-5,6,10b-triazaacephenanthrylene-2-carboni-trile (**2c**). Procedure A; Yield: (0.33 g, 91.3%), mp 288-290 °C. IR: 3299, 3132, 3057, 2978, 2926, 2215, 1719, 1618, 1579 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$), δ 8.95 (s, 1H, NH), 7.95 (m, 1H, H-7), 7.65 (m, 1H, H-8), 7.63 (m, 1H, H-9), 10.35 (m, 1H, H-10), 7.68 (d, 2H, H-32,36), 7.54 (t, 2H, H-33,35), 7.55 (t, 1H, H-33), 7.46 (d, 2H, *J* = 9 Hz, H-52,56), 7.01 (d, 2H, *J* = 9 Hz, H-53,55), 4.08 (q, 2H, *J* = 7 Hz, OCH_2), 1.44 (t, 3H, *J* = 7 Hz, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$), δ 156.8 (C-1), 133.8 (C-2), 103.8 (C-3), 98.1 (C-3a), 152.3 (C-3a[1]), 162.9 (C-4), 148.8 (C-5a), 138.5 (C-6a), 129.6 (C-7), 128.3 (C-8), 128.3 (C-9), 121.8 (C-10), 127.1 (C-10a), 130.7 (C-31), 129.1 (C-32), 128.4 (C-33), 131.3 (C-34), 124.3 (C-51), 127.9 (C-52), 115.0 (C-53), 158.6 (C-54), 63.8 (OCH_2), 14.8 (CH_3), 116.0 (CN). MS-ESI: *m/z* 458 (M^++1). Anal. Calcd for $C_{28}H_{19}N_5O_2$: C, 73.51; H, 4.19; N, 15.31. Found: C, 73.76; H, 4.15; N, 15.03.

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