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Tetrahedron Letters 45 (2004) 5815–5818
Tetrahedron Letters

An innovative approach to the synthesis of annelated [*a*]diaza-anthracenones through tandem cyclization ☆

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Received 21 April 2004; revised 26 May 2004; accepted 3 June 2004

Abstract—An innovative route for the synthesis of a novel class of 4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a-diazacyclopenta[*a*]anthracene-6-carbonitriles **5a**–**h** and 5-aryl-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4a-diazabenzo[*a*]anthracene-7-carbonitriles **5i**–**k** has been developed by ring transformation of suitably functionalized 2*H*-pyran-2-ones **1** with α-oxoketene cyclic aminals **2** to give compounds **4** followed by photo-induced cyclization.

Polyheterocyclic quinone[1] [(PHQ (Fig. 1) systems are known to display diverse pharmacological and industrial applications especially as anticancer agents,[2] and vat dyes.[3] The chemistry and therapeutic importance of annelated [*a*]azaanthraquinones have been explored extensively, but the synthesis and pharmacology of bridgehead annelated [*a*]diazaanthracenone (DAA) (Fig. 1) are unexplored so far.

Fused heterocyclic anthraquinones have been prepared[4,5] by heating 1-amino-2-ethynyl-9,10-anthraquinone and 1-amino-2-(1-amino-2-benzoylvinyl)-9,10-anthraquinone in piperidine separately. PHQs have been synthesized[6] by Michael addition of indole to 2,5,8-quinolinetriones followed by Diels–Alder cycloaddition in good yield. Nonannelated azaanthraquinones have been obtained either by Diels–Alder reaction of azanaphthaquinone with an appropriate diene[7] or by classical Friedel–Crafts reaction[8] or by oxidation of 9,10-dihydroazaanthracene.[9] Bridgehead annelated [*a*]diazaanthracenones (DAAs) have not been reported so far.

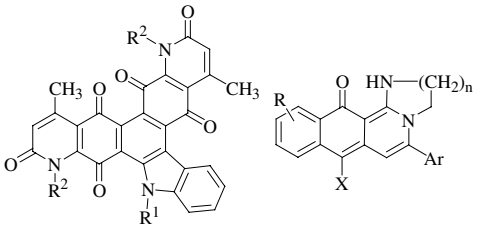

Figure 1. Chemical structure of polyheterocyclic quinones (PHQs) and diazaanthracenones (DAAs).

The presence of the 2*H*-pyran-2-one **1** unit in many natural products and its suitability for ring transformation reactions have led to its exploitation as a synthon for generating molecular diversity.[10] Herein we report a short efficient access to fused anthracenone derivatives **5** through ring transformation reactions of suitably functionalized 2*H*-pyran-2-ones **1** with α-oxoketene cyclic aminals **2** followed by photocyclization.

Our strategy to synthesize 4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a-diazacyclopenta[*a*]anthracene-6-carbonitriles **5a**–**h** and 5-aryl-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4*a*-diazabenzo[*a*]anthracene-7-carbonitriles **5i**–**k** was based on the reaction of 6-aryl-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitriles[11] **1** with α-oxo-ketene cyclic aminals **2**, obtained[12] from the reaction of α-oxo-ketenedithioacetal and diaminoalkanes (Scheme 1). Thus, stirring an equimolar mixture of **1**, **2** and powdered KOH in dry DMF for 24 h at ambient

Keywords: Photocyclization; X-ray diffraction; Ring transformation reactions; Reaction mechanism.
☆ CDRI communication no: 6523.
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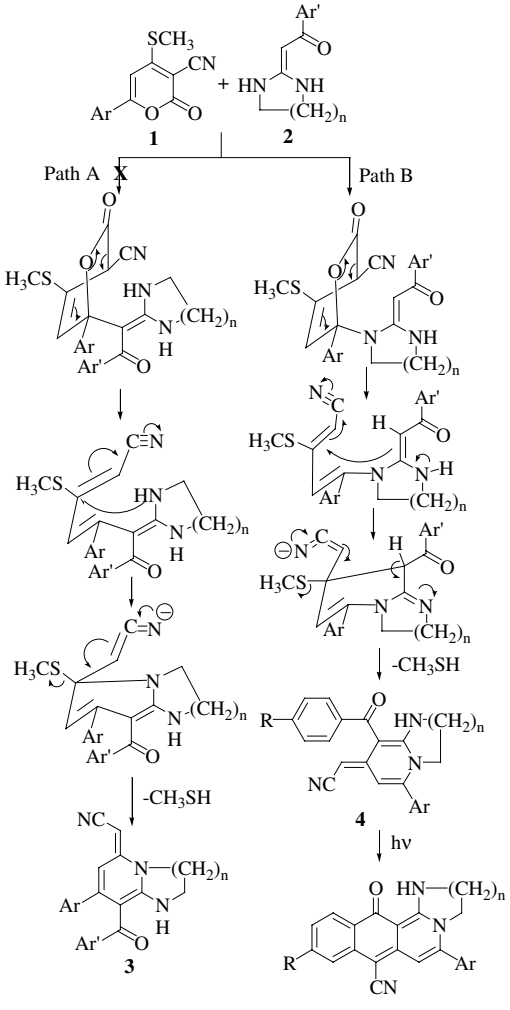
doi:10.1016/j.tetlet.2004.06.015



4/5	Ar	R	n	Yield 4	Yield 5
a	4-ClC_6H_4	H	1	65	42
b	4-BrC_6H_4	H	1	57	44
c	C_6H_5	H	1	66	52
d	C_6H_5	Cl	1	58	49
e	4-$CH_3OC_6H_4$	Cl	1	62	48
f	4-FC_6H_4	Cl	1	51	41
g	1-naphthyl	Cl	1	65	53
h	4-BrC_6H_4	Cl	1	55	52
i	C_6H_5	Br	2	64	53
j	4-BrC_6H_4	Br	2	55	46
k	4-$CH_3C_6H_4$	Br	2	61	54

Scheme 1. Proposed mechanism for the formation of **5**.

temperature and usual work-up led to **5** directly but in very poor yield (5%). Thus, attempts were made to isolate any intermediates to understand the course of the reaction as well as to improve the yield. The intermediate **4** was synthesized from the reaction of **1** and **2** and purified in the absence of direct light in ~60% yield. The photocyclization of **4** in acetonitrile yielded **5** in ~50% yield.

The nature of the ring substituents present at positions 3 and 4 of the pyran ring greatly influences the course of these reactions. An electron withdrawing substituent, especially at position 3, is an essential requirement, as such substituents enhance the electrophilicity of C6 of the pyran ring to nucleophilic attack. 2*H*-Pyran-2-ones **1** can be considered as a cyclic ketene hemithioacetal, which is prone to nucleophilic attack at C6 due to extended conjugation. α-Oxoketene cyclic aminals **2**, have three nucleophilic centres, two secondary amines and a vinylic carbon adjacent to the carbonyl function. Thus possibilities for the formation of two intermediates **3** or **4** exist, depending upon the initial participation of either of the nitrogen or carbon nucleophilic centres. Reaction through intermediate **3** was ruled out on the basis of the structure of the isolated photocyclized product **5**, which is only available from intermediate **4**. Further photoirradiation of intermediate **4** in acetonitrile with a 200 W electric bulb provided cyclized product **5** in moderate yield. In cases where photocyclized products precipitated, they were filtered off and recrystallized from a chloroform–methanol mixture, or purified by Si-gel column chromatography. The UV spectrum of a freshly prepared 0.01 mM solution of **4** in DMSO showed an absorption band at 435 nm, which completely disappeared after irradiation for 2 h with the appearance of a new absorption maximum at 385 nm (Fig. 2).

A free radical mechanism for the photochemical transformation of **4** was ruled out on the basis of the isolation of product **5** even in the presence of TEMPO free radical. Thus, the reaction possibly proceeds through a photochemically allowed conrotatory cyclization[13] followed by aerial oxidation of a dihydro intermediate to yield **5**. A plausible mechanism for this reaction involves nucleophilic attack of the secondary amine at C6 of the pyran ring with ring opening followed by decarboxylation and recyclization, involving the vinylic carbon and C4 of the pyran ring liberating methyl mercaptan to yield **4** (Scheme 1). The stereoselective formation of intermediate **4** in this reaction is possibly due to either strong intramolecular hydrogen bonding between the NH and C=O functionalities or steric hindrance, which plays an important role in restricting the rotation of the aroyl group and enforces the required *E* geometry. Intermediates **4** isolated from this reaction were characterized by IR, NMR and mass spectrometry[14] as (*E*)-2-(8-aroyl-5-aryl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-7-ylidene)acetonitrile (**4**, $n = 1$) and (*E*)-2-(9-aroyl-6-aryl-1,2,3,4-tetrahydro-8*H*-pyrido[1,2-*a*]pyrimidin-8-ylidene)acetonitrile (**4**, $n = 2$). The proton NMR spectrum of **4e** demonstrated two CH singlets at 6.33 and

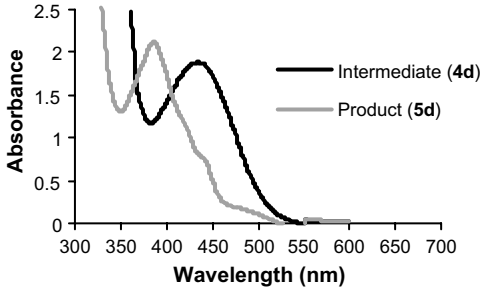


Figure 2. Absorption maxima of intermediate **4d** (435 nm) and product **5d** (385 nm) after irradiation (200 W electric bulb) for 2 h.

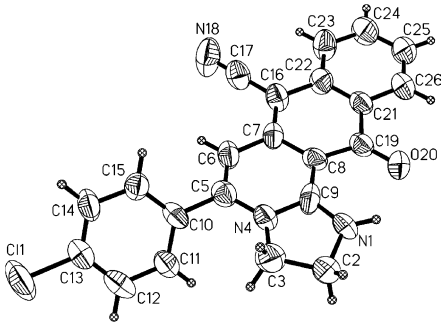


Figure 3. ORTEP diagram of **5a** showing the X-ray molecular structure at the 50% probability level.

3.59 ppm, a methyl singlet at 3.83 ppm, a set of methylene protons as a multiplet centred at 3.86 ppm, two sets of *ortho* coupled doublets at 7.34 and 7.57 ppm and a broad singlet at 8.49 ppm for the NH proton. The high field shift of the vinylic proton at 3.59 ppm and its ^{13}C chemical shift at 72.9 ppm can be attributed to the shielding effect of the carbonyl and nitrile functionalities. The structure of the photocyclized products **5** were confirmed spectroscopically[14] and also through a single crystal X-ray diffraction analysis for product **5a** (Fig. 3).[15]

The X-ray structure revealed that two rotamers 47.1° (2) and 77.4° (2) are present in one asymmetric unit. Rotamers arise due to free rotation along the aryl–aryl bond.

In summary, our methodology provides a concerted approach to the synthesis of fused heterocyclic systems in two-steps using readily available starting materials under mild conditions. It also opens an efficient synthetic route for the synthesis of complex aza heterocycles.

Acknowledgements

A.S. thanks CSIR, New Delhi, India for a Senior Research Fellowship. The authors thank SAIF, CDRI, Lucknow for providing spectroscopic and analytical data.

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14. Typical procedure for **4**: A mixture of 2*H*-pyran-2-one **1**, (1 mmol), oxoketene cyclic aminal **2** (1 mmol) and NaH (60% suspension, 2.5 mmol) in dry THF (20 mL) was stirred for 2 h at 5–10 °C in the dark. After additional stirring for another 10 h at 20–25 °C, the reaction mixture was poured into ice-water and neutralized with 10% HCl. The separated solid was filtered, washed with water and dried. The reaction was carried out in the dark to prevent photocyclization. The crude solid was further purified by column chromatography using 50% hexane–$CHCl_3$) as eluent in the dark. Compound **4e**: Yield 250 mg (62%); mp: 194–196 °C (dec.); IR (neat): $\nu = 3353, 3019, 2927, 2856, 2175, 1640, 1597, 1529, 1295, 1216, 1091, 1013\,cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.58$ (s, 1H, CH), 3.83–3.89 (m, 7H, OCH_3 and $2NCH_2$), 6.32 (s, 1H, CH), 6.95–6.98 (d, $J = 8.7$ Hz, 2H, ArH), 7.32–7.39 (m, 4H, ArH), 7.56–7.59 (d, $J = 8.4$ Hz, 2H, ArH), 8.49 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 42.7, 46.9, 55.4, 72.9, 110.7, 114.3, 122.1, 125.4, 129.6, 138.5, 149.7, 156.8, 160.7, 192.8$; FAB (MS) 404 ($M^+$+1). Typical procedure for **5**: A solution of **4** (0.05 mmol) in acetonitrile was irradiated for 10 h with a 200 W electric bulb with stirring. A yellow solid separated which was filtered and washed with methanol. The crude product was further purified by column chromatography using 1% methanol in chloroform as eluent. Compound **5h**: Yield 135 mg (52%); mp: >250 °C; IR (neat): $\nu = 3330, 2183, 1642, 1593, 1516, 1219\,cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.06–4.23$ (m, 4H, $2NCH_2$), 6.84 (s, 1H, CH), 7.28–7.40 (m, 4H, ArH), 7.67–7.71 (m, 2H, ArH), 7.91 (br s, 1H, ArH); FAB (MS) 451 (M^++1); $C_{22}H_{13}BrClN_3O$ (450.71) calcd C 58.63, H 2.91, N 9.32; found C 58.71, H 3.05, N 9.62.
15. Crystal data of **5a**: $C_{22}H_{14}Cl_1N_3O_1$, $M = 371.81$, orthorhombic, space group *Pbca*, $a = 15.978(2)$, $b = 17.408(2)$, $c = 25.366(2)$ Å, $V = 7055.4(13)$ Å^3, $T = 293$ K, $Z = 8$, $\mu = 0.23\,mm^{-1}$, $R1 = 0.0804$ for 1644 Fo >4 sig(Fo) and

0.3330 for all 6204 data. CCDC 233580 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997].