SYNTHESIS OF FURO- THIENO- AND PYRROLO- [3,2-a]ACRIDONES

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Abstract: Furo-, thieno- and pyrrolo[3,2-a]acridones, that could be conveniently prepared in two step process from 4-hydroxy-2-methylquinoline, is reported. All the synthesized heterocycles have been fully characterized by IR, ^{1}H NMR and Mass Spectroscopy.

Introduction

Irradiation with UV-light has now been established as useful method in the construction of carbocyclic[1,2] as well as heterocyclic[3,4] ring systems from appropriate substrates. Among the photo-induced cyclizations, conversion of 1,3,5-hexatriene system to a cyclohexadiene system[5,6] has been established to proceed via., initial photo-isomerisation of a E-isomer to the Z-isomer in which, its S_1-state undergoes orbital symmetry-controlled conrotatory ring closure to give the cyclohexadiene system in presence of oxidizing agents like iodine, ferric chloride etc. A retrace on the photo-induced cyclizations, as witnessed with various types of compounds bearing the 1,3,5-hexatriene system such as stilbenes, azobenzenes etc., would evoke considerable interest in extending it to the synthesis of some acridine derivatives due to their significant biological properties[6,7].

Experimental

Melting points were determined on a Boetius Microheating Table and Mettler-FP5 Melting-point apparatus and are uncorrected. IR spectra were recorded on a shimadzu-8201 FT instrument in KBr disc. ^{1}H NMR spectra were recorded on a AMX-400 MHz spectrometer in DMSO-d_6 solution; chemical shifts are expressed in ppm (δ) relative TMS, coupling constants (J) in Hz. Mass spectra were recorded on a Jeol-300 mass spectrometer. Column chromatography was performed on either neutral alumina (~150 mesh) or silicagel (60-120 mesh). Irradiation was carried out in quartz tubes using a preparative photoreactor fitted with 253.7 nm UV-lamps.

Condensation of 4-hydroxy-2-methylquinoline with aldehydes

General procedure

Equal mole of 4-hydroxy-2-methylquinoline and the respective aldehydes in freshly distilled acetic anhydride (10 mL) was refluxed at 145°C for 10-20 hrs. After cooling, the reaction mixture was poured into crushed

ice. The precipitated product was filtered, dried and purified by neutral alumina column chromatography ($CHCl_3$:MeOH). All the compounds are yellow in colour and melted above 300^0C.

Cyclization by Irradiation

General procedure

Compound (0.5 m mole) was dissolved in a 2:1 mixture of benzene: methanol (150 mL), a catalytic amount of iodine was added and the solution was irradiated for 48 hrs. The residue from the solvent evaporation was purified by silica gel column chromatography (Pet. ether: EtOAc). All the compounds are yellow in colour and melted above 300^0C.

Results and Discussion

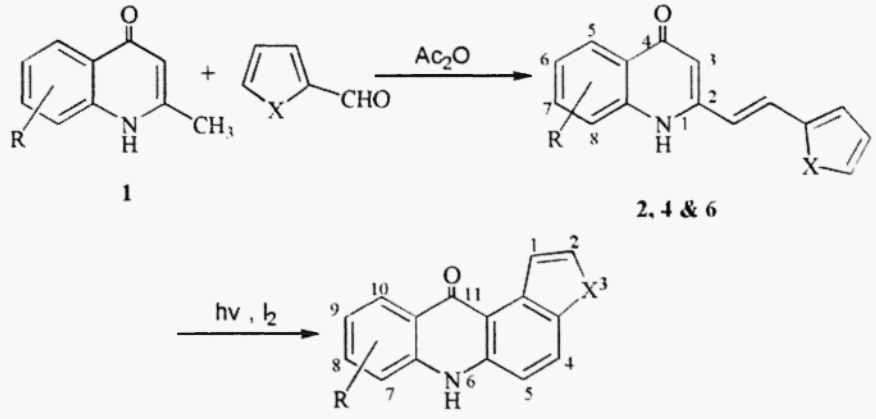
The synthesis commenced with the condensation of 4-hydroxy-2-methylquinoline 1a with furfural in acetic anhydride which afforded a yellow coloured synthon 2a in 67% yield (mp >300°C). IR spectrum of 2a exhibited an absorption band at 1641 cm^{-1} ascribable to 4-quinolone moiety and broad NH absorption at 3060-3255 cm^{-1} region. In ^{1}H NMR, signals at δ 6.35 (s, 1H, H-3) and at δ 6.8 & 7.5 (2d, 2x1H, J=16 Hz) of olefinic protons suggested that the condensation has taken place on the methyl group of the quinoline. The other signals were at δ 6.6-7.8 (m, 6H), 8.03-8.05 (d, 1H, J=8.2 Hz, H-5) and 11.5 (s, 1H, NH). The mass spectrum illustrated the fragments as at m/z 237 (M^+), 210 (M^+-HCN), 209 (M^+-CO), 184 (M^+-(HCN+C_2H_2)). The elemental analysis C 75.8, H 4.7, N 5.9 agreed well with the molecular formula $C_{15}H_{11}NO_2$. All the above spectral data accredited the compound 2a as 2[2(2-furylethenyl)quinolin-4(1H)-one (Scheme 1).

In our attempt to utilizing the photocyclization in the synthesis of acridines, we irradiate the benzene: methanol (2:1) solution of 2a containing the oxidant iodine. The evaporation of the solvent followed by silica gel column chromatography gave the product 3a (yield:40%; mp >300°C) which registered IR absorptions at 1645 cm^{-1} and 3100-3300 cm^{-1} for >C=0 and NH groups respectively. The ^{1}H NMR clearly pictured the disappearance of singlet at δ 6.35 which indicated the loss of the C_3-proton due to the cyclization. All the aromatic protons gave multiplet at 7.17 8.27. A low field resonance at δ 8.45 corresponding to H-1 was clearly identified as it anisotropically deshielded by the effect of the >C=0 bond. The mass spectrum showed the molecular ion peak at m/z 235 along with other fragment ions peak at m/z 207 (M^+-CO), 206 (M^+-(CO+H)), 180, 152 and 125 characterized the furoacridone system. These spectral data confirmed the structure of 3a as furo[3,2-a]acridin-11(6H)-one (scheme 1).

Having achieved the synthesis of furo[3,2-a]acridone, we employed the same photocylization reaction in the synthesis of theino- and pyrrolo- [3,2-a] acridones (Scheme 1). All the derivatives of compounds 4, 6 and 5, 7 revealed the same pattern of IR and ^{1}H NMR as that of 2 and 3 respectively. Theino derivatives were obtained in fair yield in condensation as well as in cyclization. But the preparation of pyrrolo derivatives showed poor yield in both the steps.

The work described here indicates a versatile reaction applicable to the easy synthesis of heterocyclic fused acridones.

SCHEME 1



1 **2, 4 & 6** **3, 5 & 7**

1,2,4,6	**a**: R = H	**3,5,7**	**a**: R = H
	b: R = 6-CH_3		**b**: R = 9-CH_3
	c: R = 8-CH_3		**c**: R = 7-CH_3
	d: R = 6-Br		**d**: R = 9-Br
	e: R = 6-Cl		**e**:R = 9-Cl

	2 & 3	**4 & 5**	**6 & 7**
X	O	S	NH

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Table I. Spectral data of Compunds 2 & 3

Compd	Yield (%)	IR (cm^{-1})	MS (70eV) m/e (M^+)	Molecular formula	Analysis calcd	Analysis found	^{1}H NMR (DMSO-d_6) δ
2a	67	3255-3060(NH) 1641 (C=O)	237	$C_{15}H_{11}NO_2$	C 75.9 H 4.6 N 5.9	75.8 4.7 5.9	6.35 (s, 1H, C_3-H), 6.8 & 7.5 (2d, 2x1H, J=16Hz, olefinic-H), 6.6-7.8 (m, 6H, Ar-H), 8.03-8.05 (d, 1H, J=8.2 Hz, C_5-H) and 11.15 (s, 1H, NH)
2b	76	3200-3089(NH) 1639 (C=O)	251	$C_{16}H_{13}NO_2$	C 76.5 H 5.1 N 5.6	76.4 5.3 5.7	2.5 (s, 3H,C_6-CH_3) 6.3 (s, 1H, C_3-H), 6.8 & 7.4 (2d, 2x1H J=15.8Hz, olefinic-H), 6.64-7.54 (m, 5H, Ar-H), 7.84 (s, 1H, C_5-H) and 11.4 (s, 1H, NH)
2c	60	3250-3100(NH) 1645 (C=O)	251	$C_{16}H_{13}NO_2$	C 76.5 H 5.1 N 5.6	75.5 5.2 5.7	2.5 (s, 3H,C_8-CH_3), 6.5 (s, 1H, C_3-H), 7.2 & 7.4 (2d, 2x1H J=16.2Hz, olefinic-H), 6.64-7.92 (m, 5H, Ar-H), 7.94 (d, 1H, J=7.9 Hz, C_5-H) and 10.4 (s, 1H, NH)
2d	66	3210-3099(NH) 1643 (C=O)	315	$C_{15}H_{10}BrNO_2$	C 57.1 H 3.2 N 4.4	57.3 3.2 4.5	6.4 (s, 1H, C_3-H), 7.1 & 7.4 (2d, 2x1H, J=16Hz, olefinic-H), 6.65-7.70 (m, 5H, Ar-H), 8.1 (s, 1H, C_5-H) and 11.2 (s, 1H, NH)
2e	55	3250-3101(NH) 1644 (C=O)	271	$C_{15}H_{10}ClNO_2$	C 66.4 H 3.6 N 5.1	66.2 3.4 5.3	6.16 (s, 1H, C_3-H), 7.2 & 7.5 (2d, 2x1H, J=16Hz, olefinic-H), 6.70-7.90 (m, 5H, Ar-H), 8.1 (s, 1H, C_5-H) and 10.4 (s, 1H, NH)
3a	40	3300-3100(NH) 1645 (C=O)	235	$C_{15}H_9NO_2$	C 76.6 H 3.8 N 5.9	76.2 3.7 5.8	7.17-8.27 (m, 7H, Ar-H), 8.45 (d, 1H, C_1-H) and 11.1 (s, 1H, NH)
3b	55	3260-3098(NH) 1642 (C=O)	249	$C_{16}H_{11}NO_2$	C 77.1 H 4.4 N 5.9	77.2 4.3 5.8	2.1 (s, 3H, C_9-CH_3), 7.14-8.2 (m, 6H, Ar-H), 8.45 (d, 1H, C_1-H) and 11.1 (s, 1H, NH)
3c	46	3300-3090(NH) 1641 (C=O)	249	$C_{16}H_{11}NO_2$	C 77.1 H 4.4 N 5.9	77.2 4.3 5.8	2.6 (s, 3H, C_7-CH_3), 6.5-7.6 (m, 6H, Ar-H), 8.25 (d, 1H, C_1-H) and 10.5 (s, 1H, NH)
3d	35	3254-3060(NH) 1645 (C=O)	313	$C_{15}H_8BrNO_2$	C 57.3 H 2.5 N 4.5	57.2 2.8 4.4	7.2-8.1 (m, 6H, Ar-H), 8.3 (d, 1H, C_1-H) and 11.4 (s, 1H, NH)
3e	41	3300-3100(NH) 1643 (C=O)	269	$C_{15}H_8ClNO_2$	C 66.9 H 2.9 N 5.2	66.7 2.8 5.3	6.69-8.06 (m, 6H, Ar-H), 8.1 (d, 1H, C_1-H) and 10.5 (s, 1H, NH)

Table II. Spectral data of compounds 4 & 5

Compd	Yield	IR (cm^{-1})	MS (70eV) m/e (M^+)	Molecular formula	Analysis calcd	found	^1H NMR (DMSO-d_6) δ
4a	84	3300-3100(NH) 1633 (C=O)	253	$C_{15}H_{11}NOS$	C 71.1 H 4.4 N 5.5	71.2 4.5 5.5	6.46 (s, 1H, C_3-H), 6.9 & 7.9 (2d, 2x1H, J=15.5 Hz, olefinic-H), 7.06-7.90 (m, 6H, Ar-H), 8.1 (d, 1H, J=7.5 Hz, C_5-H) and 11.6 (s, 1H, NH)
4b	93	3250-3000(NH) 1632 (C=O)	267	$C_{16}H_{13}NOS$	C 71.9 H 4.9 N 5.2	71.8 4.8 5.1	2.5 (s, 3H C_5-CH_3), 6.4 (s, 1H, C_3-H), 6.9 & 7.9 (2d, 2x1H, J=16 Hz, olefinic-H), 7.22-7.90 (m, 6H, Ar-H) and 11.5 (s, 1H, NH)
4c	86	3350-3100(NH) 1635 (C=O)	267	$C_{16}H_{13}NOS$	C 71.9 H 4.9 N 5.2	71.7 4.9 5.1	2.6 (s, 3H, C_8-CH_3), 6.6 (s, 1H, C_3-H), 7.3 & 7.9 (2d, 2x1H, J=16.5 Hz, olefinic-H), 7.22-8.1 (m, 6H, Ar-H) and 10.5 (s, 1H, NH)
4d	84	3330-3150(NH) 1632 (C=O)	332	$C_{15}H_{10}BrNOS$	C 54.5 H 3.0 N 4.2	54.5 3.2 4.0	6.5 (s, 1H, C_3-H), 7.1 & 7.9 (2d, 2x1H, J=16Hz, olefinic-H), 7.32-8.2 (m, 6H, Ar-H) and 11.2 (s, 1H, NH)
4e	80	3250-3150(NH) 1635 (C=O)	287	$C_{15}H_{10}ClNOS$	C 62.7 H 3.4 N 4.8	62.7 3.5 4.3	6.6 (s, 1H, C_3-H), 7.2 & 7.9 (2d, 2x1H, J=15.5Hz, olefinic-H), 7.2-8.4 (m, 6H, Ar-H) and 10.1 (s, 1H, NH)
5a	41	3310-3150(NH) 1632 (C=O)	251	$C_{15}H_9NOS$	C 71.7 H 3.5 N 5.5	71.8 3.7 5.6	7.5-8.4 (m, 7H, Ar-H), 8.9 (d, 1H, C_1-H) and 11.7 (s, 1H, NH)
5b	52	3400-3150(NH) 1635 (C=O)	265	$C_{16}H_{11}NOS$	C 72.4 H 4.1 N 5.2	72.3 4.3 5.4	2.6 (s, 3H, C_9-CH_3), 7.6-8.4 (m, 6H, Ar-H), 8.9 (d, 1H, C_1-H) and 12.1 (s, 1H, NH)
5c	45	3400-3100(NH) 1633 (C=O)	265	$C_{16}H_{11}NOS$	C 72.4 H 4.1 N 5.2	72.4 4.1 5.0	2.5 (s, 3H, C_7-CH_3), 7.7-8.3 (m, 6H, Ar-H), 8.5 (d, 1H, C_1-H) and 10.9 (s, 1H, NH)
5d	39	3355-3155(NH) 1631 (C=O)	330	$C_{15}H_8BrNOS$	C 54.5 H 2.4 N 4.2	54.5 2.2 4.1	6.9-8.2 (m, 6H, Ar-H), 8.8 (d, 1H, C_1-H) and 10.3 (s, 1H, NH)
5e	42	3465-3200(NH) 1631 (C=O)	285	$C_{15}H_8ClNOS$	C 63.1 H 2.8 N 4.9	63.2 2.9 4.7	6.7-7.8 (m, 6H, Ar-H), 8.3 (d, 1H, C_1-H) and 9.9 (s, 1H, NH)

Table III. Spectral data of compounds 6 & 7

Compd	Yield	IR (cm^{-1})	MS (70eV) m/e (M^+)	Molecular formula	Analysis calcd	Analysis found	^1H NMR (DMSO-d_6) δ
6a	42	3250-3000(NH) 1639 (C=O)	236	$C_{15}H_{12}N_2O$	C 76.2 H 5.1 N 11.8	76.3 5.0 11.9	6.5 (s, 1H, C_3-H), 6.7 & 7.5 (2d, 2x1H, J=15 Hz, olefinic-H), 7.1-8.1 (m, 6H, Ar-H), 8.2 (d, 1H, J=7.5 Hz, C_5-H), 11.4 (s, 1H, NH) and 11.8 (s, 1H, NH)
6b	52	3300-3000(NH) 1641 (C=O)	250	$C_{16}H_{14}N_2O$	C 76.8 H 5.6 N 11.2	76.9 5.7 11.1	2.5 (s, 3H C_6-CH_3), 6.7 (s, 1H, C_3-H), 6.8 & 7.7 (2d, 2x1H, J=16 Hz, olefinic-H), 7.0-8.2 (m, 6H, Ar-H), 8.2 (d, 1H, J=7.8 Hz, C_5-H), 11.1 (s, 1H, NH) and 11.4 (s, 1H, NH)
6c	48	3300-3150(NH) 1645 (C=O)	250	$C_{16}H_{14}N_2O$	C 75.8 H 5.6 N 11.2	76.9 5.7 11.2	2.6 (s, 3H C_8-CH_3), 6.6 (s, 1H, C_3-H), 6.9 & 7.9 (2d, 2x1H, J=16.5 Hz, olefinic-H), 7.2-8.4 (m, 6H, Ar-H), 10.9 (s 1H, NH) and 11.2 (s, 1H, NH)
6d	38	3330-3100(NH) 1645 (C=O)	314	$C_{15}H_{11}BrN_2O$	C 57.1 H 3.5 N 8.8	57.0 3.3 8.6	6.8 (s, 1H, C_3-H), 7.2 & 7.9 (2d, 2x1H, J=16Hz, olefinic-H), 7.3-8.6 (m, 6H, Ar-H), 11.1 (s, 1H, NH) and 11.3 (s, 1H, NH)
6e	40	3250-3100(NH) 1644 (C=O)	270	$C_{15}H_{11}ClN_2O$	C 66.6 H 4.0 N 10.3	66.4 4.2 10.2	6.6 (s, 1H, C_2-H), 7.1 & 7.9 (2d, 2x1H, J=15.5Hz, olefinic-H), 7.2-8.4 (m, 6H, Ar-H), 11.1 (s, 1H, NH) and 11.2 (s, 1H, NH)
7a	30	3300-3190(NH) 1645 (C=O)	234	$C_{15}H_{10}N_2O$	C 76.9 H 3.8 N 11.9	76.8 3.7 11.8	7.0-8.9 (m, 8H, Ar-H), 11.1 (s, 1H, NH) and 11.3 (s, 1H, NH)
7b	32	3300-3150(NH) 1640 (C=O)	248	$C_{16}H_{12}N_2O$	C 77.4 H 4.4 N 11.2	77.3 4.3 11.4	2.5 (s, 3H, C_9-CH_3), 7.7-8.5 (m, 7H, Ar-H), 11.9 (s, 1H, NH) and 12.1 (s, 1H, NH)
7c	31	3300-3150(NH) 1640 (C=O)	248	$C_{16}H_{12}N_2O$	C 77.4 H 4.4 N 11.2	77.3 4.4 11.1	2.6 (s, 3H, C_7-CH_3), 7.9-8.9 (m, 7H, Ar-H), 10.1 (s,1H, NH) and 11.1 (s,1H, NH)
7d	29	3300-3100(NH) 1645 (C=O)	312	$C_{15}H_9BrN_2O$	C 57.5 H 3.1 N 8.9	57.3 3.2 8.8	7.5-8.9 (m, 7H, Ar-H), 10.3 (s, 1H, NH) and 10.5 (s, 1H, NH)
7e	28	3300-3100(NH) 1644 (C=O)	268	$C_{15}H_9ClN_2O$	C 67.2 H 3.7 N 10.4	67.1 3.7 10.4	7.8-8.8 (m, 7H, Ar-H), 10.5 (s, 1H, NH) and 11.2 (s, 1H, NH)