Asian Journal of Chemistry Vol. 4, No. 2 (1992) 364–371

Synthesis of Some New 2,3/2,4-Disubstituted-1,2,4-Triazino [5,6-b] Indoles

R. M. ABDEL-RAHMAN*, Z. EL-GENDY AND M. M. FAWZY

Chemistry Department, Faculty of Education
Ain-Shams University, Roxy, Cairo, AR Egypt

A number of some new 2,3/2,4-disubstituted-1,2,4-triazino [5,6-b] indoles have been synthesized, the former by the reaction of 3-hydrazone-indol-2(H)one(I), 3-(N-aroyl-hydrazone)-indol-2(H)ones(II), 2-arylamino-3-hydrazone-indoles(V) and or 2, 3-dihydrazone-1H-indole(VIII) with ammonium acetate, urea, thiourea, ethyl chloroformate and 1,1-dichloro-acetic acid. All the new compounds have been characterized by their IR, UV and PMR spectral data.

INTRODUCTION

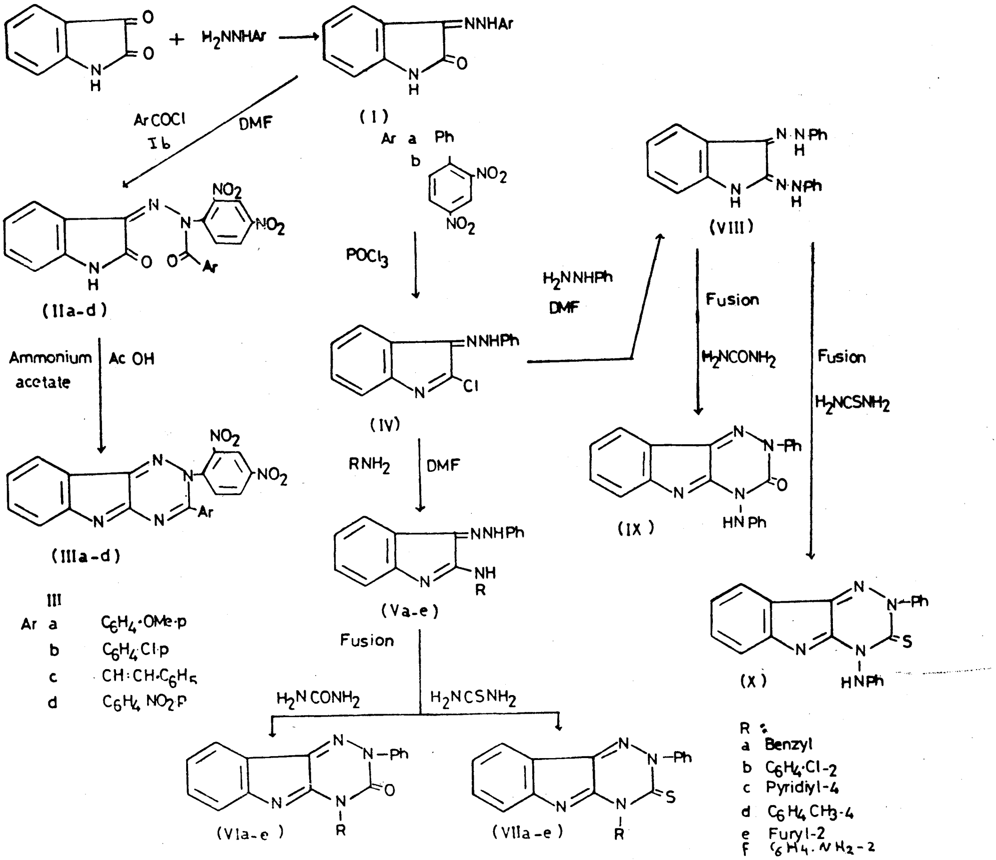
In continuation to our previous work in the area of substituted-1,2,4-triazino indoles chemistry[1,2], our interest has now been extended to the synthesis of some new 2,3/2,4-disubstituted-1,2,4-triazino[5,6-b] indoles starting from 3-hydrazoneindole derivatives.

RESULTS AND DISCUSSION

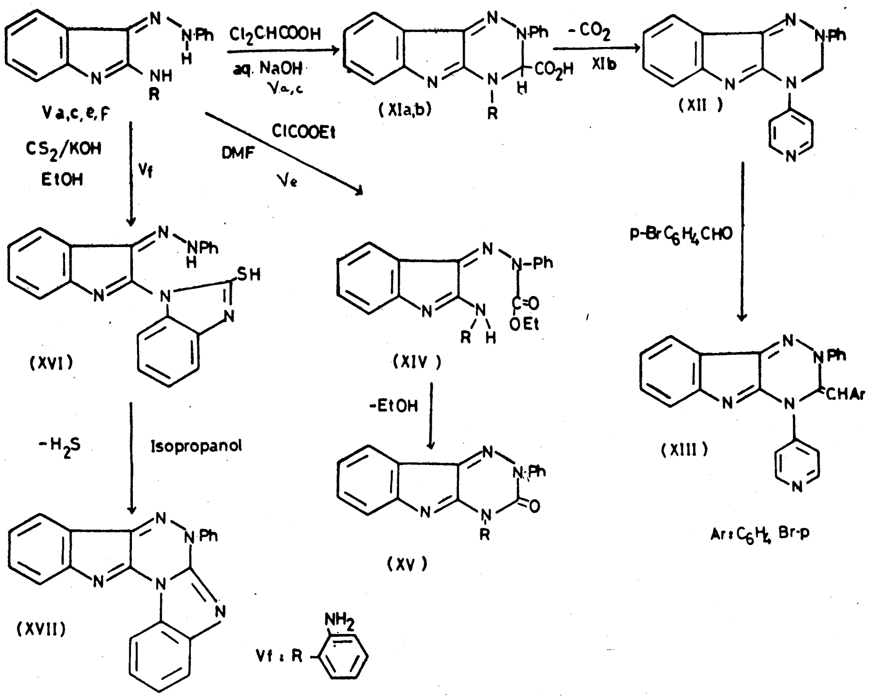
It has been observed in the present work that isatin condense with phenylhydrazine and 2,4-dinitrophenylhydrazine in the presence of methanol-acetic acid yielding the corresponding hydrazones Ia, b. Treatment of compound Ib with acid chloride in boiling DMF [3], 3-(N-aroylhydrazone)-indol-2(H)ones(IIa-d) was obtained, which fused with ammonium acetate containing a few drops of glacial acetic acid[4] yielded 2,3-diaryl-1,2,4-triazino[5,6-b] indoles(IIIa-d) [Scheme 1]. Attempts toprepare the 2-chloro-3-hydrazonindole(IVb) by refluxing Ib with $POCl_3$ or PCl_5-$POCl_3$ mixture, failed, while Ia was converted into 2-chloro-3-(N-phenylhydrazone)-indole (IV) by refluxing with $POCl_3$ only. Aminolysis of IV by using primary amines in the presence of DMF afforded 2-arylamino-3-hydrazone-indoles (Va-f). Fusion of compounds Va-e with urea and/or thiourea led to the direct formation of 3-oxo/thioxo-2,4-diaryl-1,2,4-triazino[5,6-b]indoles (VIa-e and VIIa-d) [Scheme 1]. Hydrazinolysis of IV with phenylhydrazine in DMF afforded the 2,3-dihydrazone-1H-indole(VIII). The latter compound was also fused with urea and/or thiourea to give 3-oxo/thioxo-2-aryl-4-arylamino-1,2,4-triazino[5,6-b] indoles (IX and X) [Scheme 1].

On the other hand, cyclocondensation of 2-arylamino-3-hydrazone-indole(Vc) with 1,1-dichloroacetic acid in the presence of aq. NaOH gave[5] the corresponding 1, 2, 4-triazino-carboxylic acid XI which decarboxylated by using aq. K_2CO_3 to give 2,4-diaryl-3-dihydro-1,2,4-triazino[5,6-b] indole(XII). The structure of the latter established by condensation with *p*-bromobenzaldehyde which afforded the arylidene XIII [Scheme 2]. The reaction of compound Ve with ethyl chloroformate in DMF, gave the ethyl ester XIV which on heating above its melting point to give 3-oxo-2,4-diaryl-1,2,4-triazino[5,6-b] indole(VIe) [Scheme 2][3]. Finally, reaction of V_f with CS_2 in the presence of aq. KOH ethanol[5] gave 3-mercapto-benzimidazole derivative XV which on boiling with *iso*-propyl alcohol containing a few drops of pipridine led to the direct formation of 3-aryl-benzimidazolo[2,3-c] [1,2,4]-triazino[5,6-b] indole(XVII) [Scheme 2].

SCHEME 1



SCHEME 2



EXPERIMENTAL

All melting points are uncorrected. IR spectra are recorded (KBr) in cm^{-1} on a Beckman IR 4 spectrophotometer, UV spectra in ethanol on a Perkin Elmer (Type 550 S) UV Vis-spectrophotometer (ν_{max} in nm) and PMR spectra in DMSO d_6 on an EM 390 90 MHz NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm) [Table 1].

Condensation of isatin with hydrazine derivatives: Formation of hydrazones Ia,b

An equimolar mixture of isatine and phenylhydrazine and 2, 4-dinitrophenylhydrazine in methanol glacial acetic acid (50 ml: 50 ml) was heated under reflux for 1 hr, cooled and diluted with cold water. The resultant solid was filtered and crystallized to give Ia,b (Table 1).

3-(N-aroylhydrazone) indol-2(H) one (IIa-d)

A mixture of Ia(0.01 mol) and the appropriate acid halides (0.01 mol) in DMF (100 ml) was heated under reflux for 6 hr, cooled, poured into ice and filtered. The solid obtained was crystallized to give IIa-d (Table 1).

2,3-Diaryl-1,2,4-triazino[5,6-b]indoles (IIIa-d)

A mixture of IIa-d(0.01 mol) and ammonium acetate (5 g) in a few drops AcOH was refluxed for 8 hrs, cooled and the resultant solid triurated with little methanol and crystallized to give IIIa-d (Table 1).

2-Chloro-3-hydrazone-indole (IV)

Compound Ia(10 g) and $POCl_3$(20 ml) was heated under reflux for 1 hr, cooled and the resultant oil poured into ice and solidified. The solid obtained was recrystallized to give IV (Table 1).

Aminolysis of IV: Formation of 2-arylamino-3-hydrazone-indoles (Va-d)

A solution of IV(0.01 mol) in DMF(50 ml) was treated with appropriate primary amines (0.01 mol) and the reaction mixture refluxed for 1 hr, cooled, diluted with cold water, filtered and the residue crystallized to give Va-d (Table 1).

Fusion of Va-d with urea and thiourea: Formation of VI-a-d and VIIa-d

A mixture of Va-d (0.01 mol) and urea or thiourea (0.02 mol) was fused under reflux for 2 hr, at 160–180°, cooled and treated with aq. NaOH. The solid obtained was filtered and recrystallized to give VIa-d or VIIa-d (Table 1).

Reaction of IV with phenylhydrazine: Formation of 2,3-dihydrazone-1H-indole (VIII)

Compound VIII was obtained following the above procedure used for the formation of compounds Va-d (Table 1).

Fusion of VIII with urea or thiourna: Formation of IX and X

Compound IX and X were obtained following the above procedure used for the formation of compounds VIa-d and VIIa-d (Table 1).

Formation of 1,2,4-triazino-carboxylic acid XIa,b

A mixture of Va,c(0.01 mol) and dichloroacetic acid (0.01 mol) in aq. NaOH (10%, 50 ml) was heated under reflux for 4 hrs, cooled, diluted with cold water and acidified. The resultant solid was filtered and recrystallized to give XIa,b (Table 1).

2,4 Diaryl-3-dihydro-1,2,4-triazino [5,6-b] indole (XII)

To a solution of K_2CO_3(10 %, 100 ml) was added XIb and the reaction mixture was warmed for 1 hr, and acidified. The solid thus obtained was filtered and washed with cold water and recrystallized to give XII (Table 1).

Condensation of XII with p-bromobenzaldehyde: Formation of the arylidene XIII

A mixture of XII(0.01 mol) and p-bromobenzaldehyde (0.01 mol) in glacial acetic acid (100 ml) was heated under reflux for 2 hr, and cooled. The solid obtained was filtered and crystallized to give XIII (Table 1).

Ethyl carboxylate XIV

To a well stirred solution of V_e (0.01 mol) and DMF (50 ml), an equimolar amount of ethyl chloroformate was added dropwise at room temperature. The reaction mixture was refluxed for 4 hrs, cooled and poured into ice. The solid obtained was filtered and crystallized to give XIV (Table 1).

Cyclization of XIV: Formation of VI

Compound XIV(2 g) was heated above melting points (60° higher) for 30 min and cooled. The solid obtained was crystallized to give VI (Table 1).

Reaction of Vf with carbon disulphide: Formation of XV

To a solution of KOH in ethanol were added Vf (0.01 mol) and carbon disulphide (30 ml) and the reaction mixture was refluxed for 4 hrs, diluted with water and acidified. The resultant solid was filtered and crystallized to give XVI (Table 1).

Cyclization of XV: Formation of XVI

A mixture of XV(0.01 mol) and *iso*-propanol (100 ml) in pipridine (2 ml) was heated under reflux for 10 hrs, cooled and acidified with dil. HCl. The resultant solid was filtered and crystallized to give XVI (Table 1).

TABLE 1

PHYSICAL DATA OF COMPOUNDS (I-XVII)

Compound No.	Solvent	M. Pt. (°C)	Yield (%)	Molecular formula	Analysis % (Cl)	
					Found	Calcd
Ia	EtOH	215–216	90	$C_{14}H_{11}N_3O$		
Ib	AcOH	*ca.* 300	96	$C_{14}H_9N_5O_5$		
IIa	DMF	288–290	75	$C_{22}H_{15}N_5O_7$		
IIb	EtOH	259–260	80	$C_{21}H_{12}N_5ClO_6$	7.25	7.85
IIc	DMF	290–292	75	$C_{23}H_{15}N_5O_6$		
IId	DMF	289–290	60	$C_{21}H_{12}N_6O_8$		
IIIa	DMF	293–295	65	$C_{22}H_{14}N_6O_5$		

Table No. 1 (contd.)

Compound No.	Solvent	M. Pt. (°C)	Yield (%)	Molecular formula	Analysis % (Cl)	
					Found	Calcd
IIIb	AcOH	280–282	75	$C_{21}H_{11}N_6ClO_4$	7.65	8.16
IIIc	DMF	289–292	70	$C_{23}H_{14}N_6O_4$		
IIId	EtOH	270–271	75	$C_{21}H_{11}N_7O_6$		
IV	EtOH	179–180	80	$C_{14}H_{10}N_3Cl$	13.82	14.25
Va	EtOH	155–156	86	$C_{21}H_{18}N_4$		
Vb	EtOH	150–151	90	$C_{20}H_{15}N_4Cl$	10.1	10.51
Vc	AcOH	195–197	70	$C_{19}H_{15}N_5$		
Vd	EtOH	145–146	75	$C_{21}H_{18}N_4$		
Ve	EtOH	170–171	85	$C_{19}H_{16}N_4O$		
Vf	EtOH	174–175	65	$C_{20}H_{17}N_5$		
VIa	EtOH	137–138	65	$C_{22}H_{16}N_4O$		
VIb	AcOH	145–147	60	$C_{21}H_{13}N_4ClO$	7.23	7.25
VIc	EtOH	135–136	70	$C_{20}H_{13}N_5O$		
VId	EtOH	142–143	77	$C_{22}H_{16}N_4O$		
VIIa	AcOH	188–190	85	$C_{22}H_{16}N_4S$		
VIIb	AcOH	192–193	80	$C_{21}H_{13}N_4SCl$	8.8	9.35
VIIc	EtOH	149–150	70	$C_{20}H_{13}N_5S$		
VIId	AcOH	201–202	65	$C_{22}H_{16}N_4S$		
VIII	DMF	170–171	85	$C_{20}H_{17}N_5$		
IX	AcOH	180–182	65	$C_{21}H_{15}N_5O$		
X	DMF	248–250	76	$C_{21}H_{15}N_5S$		
XIa	EtOH	174–175	65	$C_{23}H_{18}N_4O_2$		
XIb	EtOH	189–790	70	$C_{21}H_{15}N_5O_2$		
XII	EtOH	198–199	60	$C_{20}H_{15}N_5$		
XIII	AcOH	179–180	78	$C_{27}H_{18}N_5Br$*		
XIV	Dil.EtOH	195–197	67	$C_{22}H_{20}N_4O_3$		
XV	AcOH	245–246	85	$C_{20}H_{14}N_4O_2$		
XVI	EtOH	190–192	90	$C_{21}H_{15}N_5S$		
XVII	DMF	164–165	85	$C_{21}H_{13}N_5$		

*Br, Found: 15.67. Calcd., 16.2 (%).

†Satisfactory C, H, N and S analysis have been obtained for all the compounds.

TABLE 2
CHARACTERISTIC INFRARED GROUP FREQUENCIES OF SOME NEW COMPOUNDS (ν: cm^{-1})

Compound	NH	Arom.	Aliph.	C=0	C=N	def. CH	C=S	Phenyl & Aryl groups
IIIc	—	3050	2920	—	1550	1460	—	1170, 900, 880
VIc	—	3010	—	1700	1610	—	—	1160, 990, 780
VIIa	—	3030	2800	—	1540	1450	1180	1090, 1050, 850
IX	3300–3100	3020	—	1630	1550	—	—	1150, 900
X	3300–3100	3020	—	—	1580	—	1230	1100, 1000
XIa	—	3030	2790	1670	1590	1470	—	1150, 1050
XII	—	3020	2800	—	1580	1450	—	1150, 990
XIII	—	3020	2800	—	1580	1450	—	1150, 990
XV	—	3020	2900	1680	1580	1470	—	1150, 1000
XVII	—	3010	2900	—	1590	1450	—	1150, 1000, 900

IIIc shown absorption bands at 1630 (CH = CH), 1525, 1350 (asym & sym NO_2).
XIa shown absorption bands at 3350 (OH).
XIII shown absorption bands at 1660 (CH = Ar), 680 (C–Br).

TABLE 3
H^1–NMR OF SOME NEW COMPOUNDS

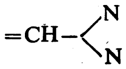
Compound	Chemical Shift	Multiplicity	Preliminary assignment
IIIc	1.7	Singlet	
	2.7	Singlet	=CH–Ph
	6–7	Multiplet	aryl, protons indole, Ph–CH
VIa	2.5	Singlet	CH_2
	5.5	Singlet	OH of 1,2,4-triazine moiety
	6.5–7.7	Multiplet	aromatic protons
IX	5.7–6.25	Multiplet	aromatic protons
	8.8	Singlet	NH–Ph
XII	2.7	Singlet	CH_2 of 1,2,4-triazine moiety
	5.5–6.25	Multiplet	aromatic protons
	6.4–7	Multiplet	pyridine protons
XIII	2.7	Singlet	=CH Aryl
	5.4–6	Multiplet	aromatic protons
	6.1–6.25	Multiplet	pyridine protons

TABLE 4

UV-ABSORPTION BANDS OF SOME NEW COMPOUNDS

Compound	$n-\pi^*$	$n-\sigma^*$	$\pi-\pi^*$	$\sigma-\sigma^*$
IIIc	375	240	225	190
VIa	380	280	240	195
	—	—	244	—
IX	380	280	240	195
XIIc	390	278	250	190
XIIIc	390	275	240	196
	—	—	230	—

REFERENCES

1. R. M. Abdel-Rahman, Z. El-Gendy and M. B. Mahmoud, *Indian J. Chem.*, **29B**, 352 (1990).
2. R. M. Abdel-Rahman, Z. El-Gendy and E. A. Mohamed, *J. Chem. Soc. Pakistan* (in press).
3. R. M. Abdel-Rahman, *Pak. J. Sci. ind. res.*, **32**, 240 (1989).
4. P. V. Laakso, R. Robison and H. P. Vandrewala, *Tetrahedron*, **1**, 103 (1957).
5. Z. El-Gendy, R. M. Abdel-Rahman, and M. S. Abdel-Malik, *Indian J. Chem.*, **28B**, 479 (1989).
6. R. M. Abdel-Rahman, A. M. Abdel-Halim, S. S. Ibrahim and E. A. Mohamed, *J. Chem. Soc. Pakistan*, **9**, **4**, 523 (1987).

[*Received*: 17 August 1990; *Accepted*: April 1991] AJC–279