Asian Journal of Chemistry Vol. 4, No. 3 (1992), 500-507

Synthesis of Some New 3,4/4,6-Disubstituted-1,2,4-Triazine-5-Ones Bearing a Pyrazolo-Pyridazine Moiety

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The synthesis of3,4-disubstituted-6-dihydro-1,2,4-triazine-5(H) one (IV), 4,6-disubstituted-1,2,4-triazine-5 (3H) ones (IX), 4,5,6-trisubstituted-3,5-dihydro-1,2,4-triazine(XII), 4,6-disubstituted-3H-5-dihydro-1,2,4-triazine (XIII) and 4-substituted-1,3,5,6-hexahydro-1,2,4-triazine(XIV) have been accomplished starting from α-hydrazinocarboxamide III and formyl-hydrazone VIII by the reaction with acid halides, α-oxoacids, α-haloketones and α,β-bihalocompounds. The structure of all new prepared compounds were elucidated on the basis of chemical and spectroscopic data.

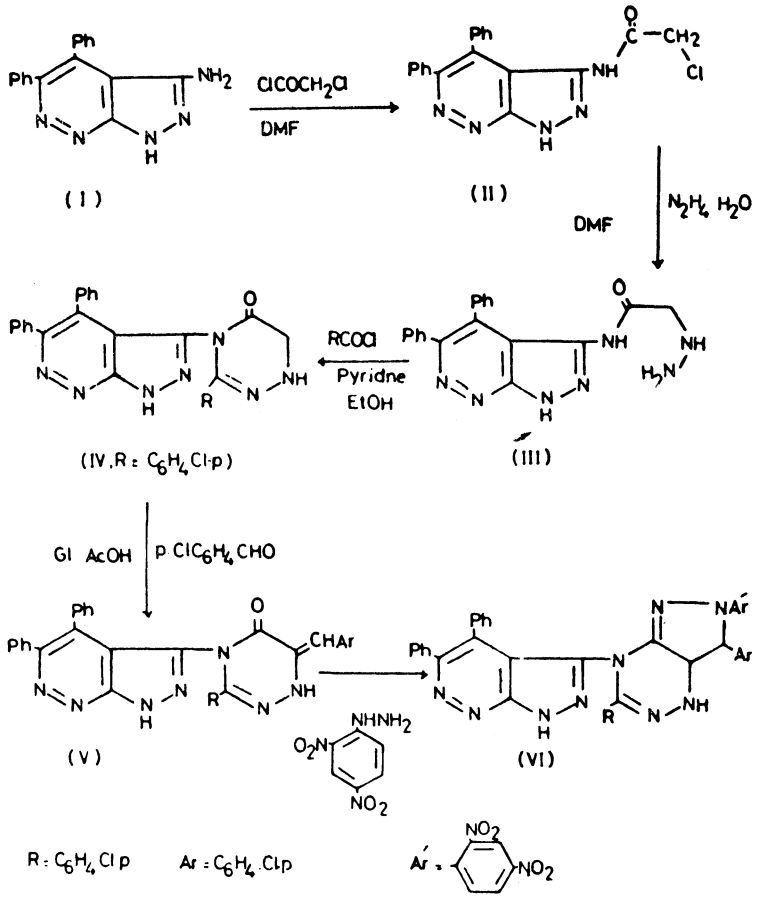
INTRODUCTION

Recently, we have reported the synthesis of 1,2,4-triazine[1-4] and pyrazolopyridazine[5] derivative, the author reports herein the synthesis of some new 3,4/4,6-disubstituted 1,2,4-triazine-5-ones bearing a pyrazolopyridazine moiety which incorporated these structural features (Scheme 1,2).

RESULTS AND DISCUSSION

3-Amino-4,5-diphenylpyrazolo[3,4-b]pyridazino (I)[5] reacts with chloroacetyl chloride in the presence of DMF to give chloroacetamide II which on treatment with hydrazine hydrate in DMF, α-hydrazinocarboxamide III obtained, which reacts with p-chlorobenzoyl chloride in pyridine abs. ethanol[6] to give 3,4-disubstituted-6-dihydro-1,2,4-triazine-5(H)-one(IV). We have elucidated the structure of compound IV by the condensation with *p*-chlorobenzaldehyde to give the arylidene V. The structure of V was completely confirmed from cyclocondensation of V with 2,4-dinitrophenylhydrazine in the presence of abs. ethanol-piperidine[7] afforded 1,4,5,9-tetrasubstituted-7,8,9-trihydropyrazolo [3,4-e] [1,2,4] triazine(VI) [Scheme 1].

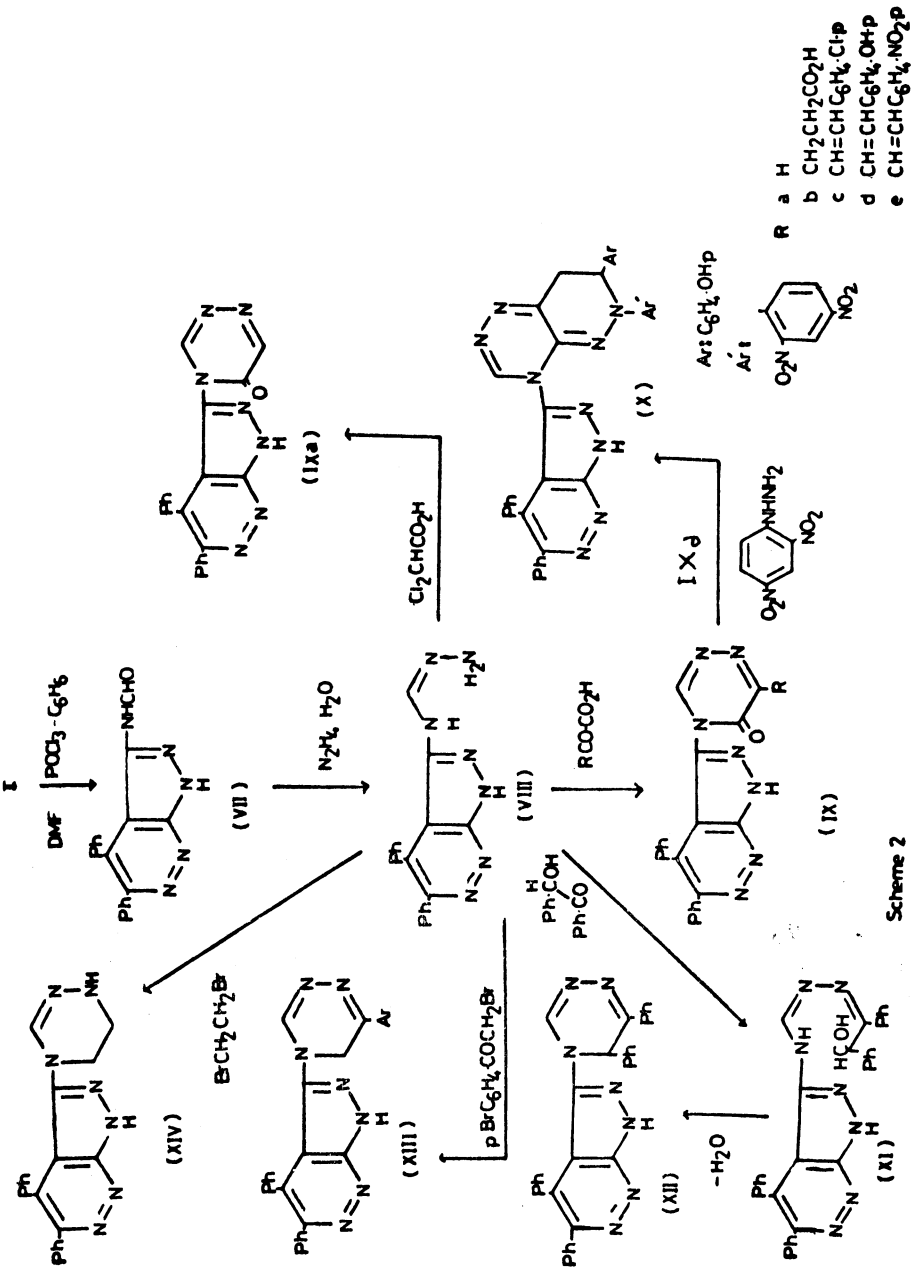
Trials to formylate I using DMF-$POCl_3$ in dry benzene adduct (Vilsmeier Haak reagent)[8] leads to the direct formation of 3-formylamino-4,5-diphenylpyrazolo[3,4-b] pyridazine (VII). Hydrazinolysis of compound (VII) gave the corresponding hydrazone (VIII) which on cyclocondensation with α-oxoacids such as, glycoxilic acid, α-oxo-glutaric acid and α-oxo-styril acids (*p*-chlorophenyl, *p*-hydroxyphenyl, *p*-nitrophenyl) in the presence of abs. ethanol[9] for long time 4,6-disubstituted-1,2,4-triazine-5 (3H)ones (IXa-e) were obtained. Compound (IX d) on refluxing with 2,4-dinitrophenylhydrazine in abs. ethanol-piperidine yielded 4,7,8-trisubsti-



Scheme 1

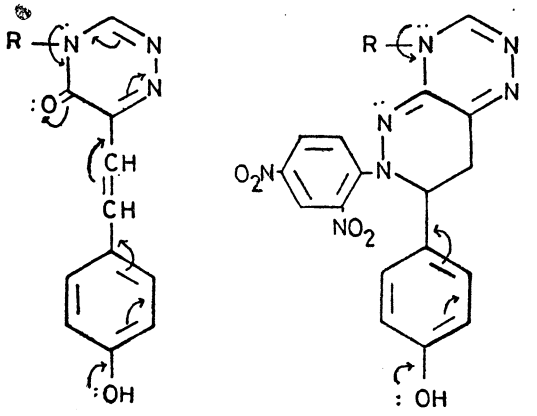
tuted-3,8,9-tetrahydro-1,2,4-triazino[5,6,c] pyridazine(X). In addition, condensation of (VIII) with benzoin gave the hydrazone (XI) which underwent cyclization by lose one mole of water, 4,5,6-trisubstituted-3,5-dihydro-1,2,4-triazine (XII) was isolated. Reaction of hydrazone (VIII) with different halocompounds have been studied, these reactions gave only isolated 1,2,4-triazine system[10]. Thus, reactions of compound (VIII) with 1,1-dichloroacetic acid, *p*-bromophenacyl bromide and 1,2-dibromoethane in the presence of ethanolic KOH, 4-substituted-1,2,4-triazin-5(3H)-one (IXa), 4,6-disubstituted-3H-5-dihydro-1,2,4-triazine(XIII) and 4-substituted-1,3,5,6-hexahydro-1,2,4-triazine(XIV) were produced [Scheme 2].

The structural assignments of compounds (IXa-e) and (X) were based on elemental analyses, IR, PMR and UV spectra. The IR and the NMR spectra rule out aromatic structure and olefinic protons. The UV spectrum



Scheme 2

also supports a highly conjugated structure [Chart I], the observed shifts



(IXd) (X)

Chart I

($\Delta\lambda_{max}$) in (IX d)-π-π* transitions of conjugated systems are found to be associated with a directional displacement of electrons towards or away from the *p*-hydroxy-phenyl ring. In addition, the n-π* transitions are observed in the case of (IX d) but these bands disappear in the case of compound (X) due to the inhibition of the conjugation systems.

EXPERIMENTAL

Melting points reported are uncorrected. UV spectra were recorded in ethanol on a Perkin Elmer (Type 550 S) UV vis spectrophotometer (λ_{max} in nm), IR spectra in KBr on a Perkin Elmer 293 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in DMSO-d_6 on a Varian EM 390 90 MHz NMR spectrophotometer using TMS as internal standard (Chemical shifts in δ, ppm). Compound (I) was prepared by the procedure described by Zaher *et al.*[5]

Reaction of I with Chloroacetyl Chloride : Formation of Chloroacetamide II

A mixture of (I) (0.01 mol) and chloroacetyl chloride (0.01 mol) in DMF (50 ml) was refluxed for 1 hr, cooled poured into cold water and filtered. The solid obtained on crystallisation gave II (Table 1); IR : 3300–2950 (NH–Ph-CH_2 broad bands), 1690–1670(C=O), 1450–1430 (def. CH_2), 1050, 850 (phenyl groups) and 710–680 (C–Cl), PMR=2.3 (s, *2H*, CH_2), 3.4 (s, *1H*, Cl–CH=C–OH), 7.1–7.4 (m, *10H*, aromatic protons) and 7.6, 7.8 (s, *1H*–NH–CO and NH– of pyrazole).

α-Hydrazinocarboxamide III

A suspension of (II) (0.01 mol) in DMF (100 ml) and hydrazine hydrate

(0.01 mol) was refluxed for 1 hr, cooled and diluted with water and filtered. The resultant solid was recrystallized to gave (III) (Table 1); IR: 3410 (NH_2), 3200, 3120 (bonded NH), 3020 (aromatic CH), 2950–2800 (aliphatic CH), 1620 (def. NH_2), 1420 (def. CH_2), 1270 (C–N), 1050, 880 (phenyl groups).

Reaction of (III) with p-Chlorobenzoyl Chloride : Formation of (IV)

A mixture of (III) (0.01 mol) and *p*-chlorobenzoyl chloride (0.01 mol) in dry pyridine (10 ml) was warmed for 15 min. and left to cool, then added abs. ethanol (100 ml). The reaction mixture was refluxed for 4 hrs, cooled and poured onto ice HCl. The separated solid was filtered, washed with cold water and crystallized to give (IV) (Table 1); IR: 3430(OH), 3250,

TABLE 1
CHARACTERIZATION DATA OF THE VARIOUS COMPOUNDS

Compd	Crystallized from	m.pt(°C)	Yield%	Mol formula	Found/(Calcd)		Cl/Br	
II	Dil.DMF	130–131	75	$C_{19}H_{14}N_5ClO$	18.5	(19.2)	9.3	(9.8)
III	EtOH	172–174	65	$C_{19}H_{17}N_7O$	26.7	(27.3)	—	—
IV	EtOH	250–251	60	$C_{26}H_{18}H_7ClO$	19.6	(20.4)	7.1	(7.5)
V	AcOH	193–195	70	$C_{33}H_{21}N_7Cl_2O$	15.8	(16.3)	11.2	(11.75)
VI	MeOH	215–216	50	$C_{39}H_{24}N_{11}Cl_2O_4$	19.1	(19.8)	8.5	(9.0)
VII	EtOH	270–272	65	$C_{18}H_{13}N_5O$	21.5	(22.2)	—	—
VIII	EtOH	243–245	75	$C_{18}H_{15}N_7$	29.0	(29.8)	—	—
IXa	EtOH	203–205	65	$C_{20}H_{13}N_7O$	25.8	(26.4)	—	—
IXb	Dil.EtOH	245–247	75	$C_{23}H_{17}N_7O_3$	21.8	(22.3)	—	—
IXc	AcOH	265–267	75	$C_{26}H_{18}N_7ClO$	18.6	(19.4)	5.35	(5.95)
IXd	AcOH	285–287	70	$C_{28}H_{19}H_7O_2$	19.5	(20.20)	—	—
IXe	DMF	288–290	75	$C_{28}H_{18}H_8O_3$	21.0	(21.7)	—	—
X	DMF	233–235	65	$C_{34}H_{24}N_{11}O_5$	22.5	(23.1)	—	—
XI	EtOH	260–261	85	$C_{32}H_{25}N_7O$	18.1	(18.73)	—	—
XII	AcOH	159–160	80	$C_{32}H_{23}N_7$	11.6	(12.27)	—	—
XIII	EtOH	230–232	65	$C_{26}H_{18}N_7Br$	18.5	(19.1)	15.1	(15.62)
XIV	Dil.DMF	230–231	60	$C_{20}H_{17}N_7$	27.1	(27.8)	—	—

3130 (NH), 3020 (aromatic CH), 2970 (aliphatic CH), 1610 (C=N), 1420 (def. CH_2) and 950, 800 (phenyl groups); PMR : 2.5 (*s*, *2H*, CH_2), 3,3 (b, *1H*,–CH=$\underset{|}{C}$–OH), 5.7 (s, *1H*, OH), 7.2–7.5 (m, *14H*, aryl protons) and 7.7, 7.8 (s: *1H*, NH of pyrazolo and 1,2,4-triazine moiety).

Condensation of (IV) with p-Chlorobenzaldehyde : Formation of (V)

An equimolar amount of (IV) and *p*-chlorobenzaldehyde in glacial acetic acid (100 ml) was refluxed for 6 hrs, cooled and diluted with cold water. The solid obtained was filtered and crystallized to give (V) (Table 1); IR : 3360 (NH), 3130 (NH), 3020 (aromatic CH), 1680 (C=O), 1600-1560 (C=C, C=N), 1430 (def. CH), 1240 (C-N), 1020, 970, 920, 850 (phenyl and aryl groups and 710-690 (C-Cl).

Cyclocondensation of (V) with 2,4-Dinitrophenylhydrazine : Formation of (VI)

An equimolar mixture of (V) and 2,4-dinitrophenylhydrazine (0.005 mol of each) in abs. ethanol (50 ml) and piperidine (0.5 ml) was refluxed for 8 hrs, cooled and poured on to ice-HCl. The resultant solid filtered and crystallized to give (VI) (Table 1); IR : 3370 (NH), 3200-3000 (NH, CH), 1610-1590 (C=N), 1510 (asy. NO_2), 1370 (sy. NO_2), 1240 (C-N), 890, 850, 795 (phenyl and aryl groups) and 700 (C-Cl).

Formylation of (I) : Formation of Formylamino Derivative (VII)

A suspension of (I) (0.01 mol) in dry benzene (20 ml) was added to a mixture of DMF (5 ml) in dry benzene (5 ml) and $POCl_3$ (3 ml) in dry benzene (5 ml). The reaction mixture was stirred for 6 hrs, left at room temperature for 24 hrs, poured onto ice, and filtered. The solid obtained was crystallized to give (VII) (Table 1); IR 3140 (NH), 3030 (aromatic CH), 2880 (aliphatic CH), 2500-2400 (CHO), 1700 (C=O), 1560 (C=N), 1420 (def. CH_2).

Hydrazinolysis of (VII) : Formation of (VIII)

A mixture of (VII) (0.01 mol) and hydrazine hydrate (0.01 mol) in abs. ethanol (50 ml) was refluxed for 1 hr, cooled. The solid obtained on crystallization gave (VIII) (Table 1); IR : 3410-3200 (NH_2, NH), 3030 (aromatic CH), 1630, 1610 (def. NH_2), 1570-1555 (C=N), 1440 (def. CH), 1220 (C-N) and 980, 790 (phenyl groups).

Cyclocondensation of (VIII) with Oxoacids : Formation of 4,6-Disubstituted-1,2,4-Triazine-5-One(IXa-e)

A mixture of (VIII) (0.01 mol) and the appropriate α-oxoacids (0.01 mol) in abs. ethanol (100 ml) was heated under reflux for 5 hrs, left overnight and diluted with cold water. The solid thus obtained was filtered and crystallized to give (IX a-e) (Table 1). Compound (IX b) gave acidity with aq. $NaHCO_3$, IR (*IXa*) : 3140 (NH), 3040 (aromatic CH), 2970 (aliphatic CH), 1660-1650 (C=O), 1560 (C=N), 1440 (def. CH), 1230 (C-N) and 970, 800 (phenyl groups), (*IX c*) : 3090 (RH), 3010 (aromatic CH), 2820 (aliphatic CH), 1730-1670 (C=O), 1610-1590 (CH=CH), 1550 (C=N) 1460 (def. CH), 1280 (C-N), 1000, 910, 850, 790 (phenyl and aryl groups) and 700 (C-Cl). (*IX d*) : 3440 (OH), 3300 (NH), 3020 (aromatic CH), 2950-

2850 (aliphatic CH), 1650–1630 (C=O), 1595–1560 (CH=CH, C=N) and 950, 880, 820 (phenyl and aryl groups). PMR : (*IX b*) : 2.5 (t, *2H*, CH_2–<), 3.3 (t, *2H*, CH_2-CO), 3.9 (s, *1H*,–CH=N in triazine ring), 6.2 (s, *1H*, OH), 7.5–6.9 (m, *10H*, aromatic protons) and 7.8 (s, *1H*, NH of pyrazole moiety), (*IX d*) : 3.7 (s, *1H*,–CH=N in 1,2,4-triazine ring), 3.9–4.2 (m, *2H* CH=CH), 5.9 (s, 1H,OH), 67–7.5 (m, *14H*, aromatic protons), and 7.7 (s, *1H*, *NH* of pyrazole moiety) : UV (IX d) : 460, 370, 275 and 200 nm.

Reaction of (VIII) with 1,1-dichloroacetic acid: Formation of (IXa)

A mixture of (VIII) (0.01 mol) and 1, 1-dichloroacetic acid (0.01 mol) in aq. NaOH (10%, 100 ml) was warmed for 1 hr, and refluxed for 4 hrs, cooled, the reaction mixture was worked as usual to give (IXa) (m.pt. and m.m.p. from above reaction gave no depration).

Cyclocondensation of (IX d) with 2,4-dinitrophenylhydrazine: Formation of (X)

The solid obtained after the same condition of formation of VI was crystallized to give compound X (Table 1); IR: 3400–3380 (OH), 3270 (NH) 3010 (aromatic CH), 2910 (aliphatic CH), 1610–1580 (C=N), 1520 (asy. NO_2), 1420 (def. CH_2), 1350 (sy. NO_2), 1270 (C–N); UV: 380, 285 and 190 nm.

Condensation of (VIII) with benzoin: Formation of (XI)

A mixture of VIII (0.01 mol) and benzoin (0.01 mol) in abs. ethanol (50 ml) in a few drops of glacial acetic acid, was refluxed for 1 hr, cooled, the solid obtained was filtered and crystallized to give XI (Table 1); IR: 3440 (OH), 3300–3120 (NH), 3040 (aromatic CH), 2980 (aliphatic CH), 1620–1590 (C=N), 1570 (C=N), 1420 (def. CH), 1270 (C–N), 1040, 960, 880 and 830 (phenyl groups).

Dehydration of (XI): Formation of (XII)

The compound (XI) was heated at 50°C above its melting points for 30 min., compound (XII) was isolated (Table 1).

Reaction of (VIII) with p-bromophenacyl bromide and 1,2-dibromethane: Formation of Compound (XIII) and (XIV)

A mixture of (VIII) (0.01 mol) and p-bromophenacyl bromide and/or 1,2-dibromoethane (0.01 mol) in ethanolic KOH (10%, 100 ml) was heated under reflux for 2 hrs. The reaction mixture was concentrated, cooled and poured onto ice HCl. The separated product was filtered and washed with cold water and crystallized to give (XIII) and/or (XIV) (Table 1); IR (*XIII*): 3090 (NH), 3000 (aromatic CH), 2900 (aliphatic), 1600–1550 (C=N), 1430 (def. CH_2), 1260 (C–N), 1020, 950, 820 (phenyl and aryl groups) and 700 (C–Br); (*XIV*): 3300, 3100 (NH, NH), 3020 (aromatic

CH), 2980, 2850 (aliphatic CH), 1600, 1550 (C=N), 1420 (def. CH_2), 1030, 950, 870 (phenyl groups). PMR (*XIV*): 2.4 (s, *2H*, CH_2—N), 3.1–3.4 (s, *2H*, CH_2–NH), 4.1 (s, *1H*, CH=N), 7.0–7.4 (m, *10H*, aromatic protons) and 7.7 (s, *1H*, NH of pyrazole), 7, 8 (s, *1H*, NH of 1,2,4-triazine).

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(*Received*: 14 November 1990; *Aecepted*; 10 March 1991) AJC-304