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Reaction of 3-Hydrazone-5,6-Diphenyl-1,2,4-Triazines with Various Activating Agents

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The reaction of 3-hydrazone-5,6-diphenyl-1,2,4-triazines(III) with various activating agents such as bases, chalcones, acrylonitrile, maleic anhydride, bromine, phenylmagnesium bromide acid halides and reduction with zinc in acetic acid have been studied. Spectroscopic data are given in support of the structure of the products.

INTRODUCTION

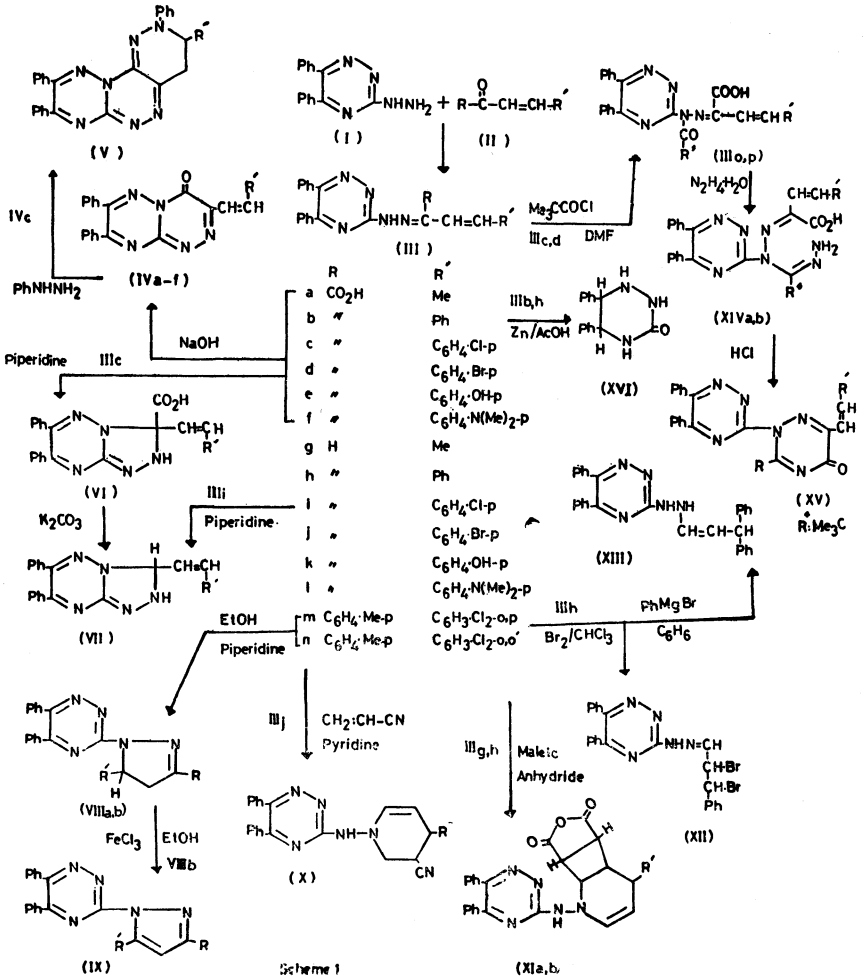
The chemistry of 1,2,4-triazine derivatives is receiving much attention in recent years. This is mainly due to the unique physical, chemical and pharmacological properties of such compounds. In continuation of the work done earlier on 5,6-diphenyl-1,2,4-triazine derivatives[1–5], the reactions of 3-hydrazone-5,6-diphenyl-1,2,4-triazines with various activating agents were reported. These reactions is depicted in Scheme 1.

RESULTS AND DISCUSSION

The starting-3-hydrazone-5,6-diphenyl-1,2,4-triazines(IIIa–f) have been synthesized from condensation of the corresponding 3-hydrazino-5, 6-diphenyl-1,2,4-triazine(I) with some α-ketoacids(IIIa–f) in abs. ethanol. Compounds IIIg–l were prepared by refluxing IIIa–f with aq. K_2CO_3, while compounds IIIm, n obtained from condensation of 3-hydrazino-triazine I with chalcones IIn, m in abs. ethanol. On the other hand, the hydrazones IIIo, p have been obtained from interaction of compounds IIId, e with pivaloyl chloride in DMF. Structures of the resulting hydrazones are supported by their UV, IR and NMR spectral data.

Treatment of compounds IIIa–f with aq. NaOH resulting in the formation of 3-cinnamoyl-6, 7-diphenyl-1, 2, 4-triazino [4, 3-b] [1, 2, 4] triazin-4-ones (IVa–f). Cyclocondensation of compound IVc with phenyl hydrazine in ethanol-piperidine yielded[3] trihydropyridazino [3, 4-e][1, 2,4] triazino [4, 3–b] [1, 2, 4] triazine derivative(V).

Cycloaddition reactions of compound III using piperidine-ethanol have been studied. Thus, compound IIIc when refluxed with ethanol-pieridine afforded 2H-3-(carboxy)-cinnamoyl-6,7-diphenyl-s-triazolo [4, 3–b]-[1, 2, 4] triazine (VI) which underwent heating with aq. K_2CO_3 to give



Scheme 1

2,3-dihydro-3-cinnamoyl-6,7-diphenyl-s-triazalo [4,3–b] [1,2,4] triazine (VII). The latter compound was also obtained from refluxing IIIi with ethanol-piperidine. 3-(3,5-Disubstituted-4,5-dihydropyrazolin-l-yl)-5,6-diphenyl-1,2,4-triazines(VIIIa, b) were obtained from compounds IIIm,n under the same above condition. The structure proof of the compound VIIIm was accomplished by oxidation with $FeCl_3$-EtOH[6] to give 3-(3,5-disubstituted-pyrazolin-l-yl)-5,6-diphenyl-1,2,4-triazine(IX).

The reactivity of the exocyclic C = C conjugated with C = N bonds in compound III were investigated by its behaviour towards the action of activated alkenes, maleic anhydride, Grignard reagents and or bromine.

Thus, IIIj reacted with acrylonitrile in pyridine-water[7] to give 1-(5, 6-diphenyl-1, 2, 4-triazin-3-ylamino)-3-cyano-4-p-bromophenyl-2, 3, 4-tetrahydropyridine(X), while addition of maleic anhydride to compounds IIIg, h in dry benzene led to the formation of the adducts products XIa, b but when this reaction was carrid out with compound IIIf, 3-cinnamoyl-7, 8-diphenyl-1, 2, 4-triazino [4, 3–b] [1, 2, 4] triazin-4-one(IVf) was isolated.

The Grignard reaction involves a nucleophilic attack at one of the electron deficient positions followed by electron shift to 1, 2 and/or 1, 4-addition[8]. Thus, phenyl magnesium bromide reacts at room temperature with compound IIIh to give compound XII via the 1, 4-addition. On the other hand, addition of bromine to compound IIIh in presence of $CHCl_3$ gave the dibromide XIII through the addition on exocylic C=C. Structure of XII and XIII were deduced from elemental analyses and spectral studies specially UV data.

The behaviour of compounds IIIe, d toward acylating agents such as, pivaloyl chloride in the presence of DMF have been investigated. In both the cases N-monoacyl IIIo, p were obtained. Hydrazinolysis of IIIo, p by refluxing with hydrazine hydrate in abs. ethanol give the hydrazones XIVa, b which underwent cyclization by refluxing with conc HCl[9] led to the direct formation of 2-(5, 6-diphenyl-1, 2, 4-triazin-3-yl)-3, 6-disubstituted-1, 2, 4-triazin-5-ones(XVa, b). The latter reaction probably proceeds via the formation of the amine salt intermediate followed by cyclization through loss of one mole of $NH_2OH.HCl$.

The attempted reduction of compounds IIIa, b, g, h and IVa, b with zinc dust and glacial acetic acid in ethanol led to the isolation one compound identified as 5, 6-diphenyltetrahydro-1, 2, 4-triazin-3 (2H) one (XVI). Structure (XVI) was finally established by direct comparison (m. m. pt.) with authentic samples prepared[10].

EXPERIMENTAL

Melting points reported are uncorrected, UV spectra recorded in DMF on a Perkin Elmer Lambda 3B Quartz (cell/cm) (λ_{max} in nm), IR spectra on Perkin Elmer SP 1430 (ν_{max} in cm^{-1}) and H^1—NMR spectra in DMSO D_6 solution with TMS as internal standard (δ, ppm) are recorded on an JNM PMX 60 NMR Spectrometer (JEOL). Halogen elements was determind by X-ray (Fluorescence Effect).

3-Hydrazone-5, 6-diphenyl-1,2,4-triazines (IIIa–p)

(i) Formation of IIIa–f : A mixture of I(0.01 mol) and appropriate α-ketoacids(II) in abs. ethanol (50 ml) was refluxed for 1 hr, cooled and diluted. The solid thus obtained was filtered and crystallized from an appropriate solvent to give IIIa–p (Table 1); IR(IIIc) : 3450 (OH), 3300–

3250 (b, NH), 3000 (aromatic CH), 2950 (aliphatic CH), 1700–1680 (C=O), 1600–1500 (b, C=C, C=N),1480–1440 (def. CH), 1000, 960 (phenyl groups) and 700 (C—Cl); (IIId) : 3500–3400 (b, OH), 3150 (NH), 3020 (aromatic CH), 2950, 2900 (aliphatic CH), 1700–1660 (C=O), 1600–1500 (b, C=C, C=N), 1480, 1440 (def. CH), 1000, 950, 850 (phenyl groups) and 700 (C—Br); (IIIi) : 3500–3100 (b, NH), 3020 (aromatic CH), 2950 (aliphatic CH), 1620 (C=C), 1560–1510 (C=N), 1020, 900, 850 (phenyl groups) and 700 (C—Cl). UV (IIIc): 360, 285 and 260, (IIIi) : 345 and 260. PMR (IIIi) : 2.7 (s, 1H, – CH=N), 4–4.2 (s, 2H, —CH=CH—), 7.3–7.6 (m, 14H, aromatic protons) and at 13 (s, 1H, NH).

(ii) Formation of IIIg—l : A suspension of IIIa–f (0.01 mol) in aq. K_2CO_3 (10%, 100 ml) was heated under reflux for 20 min.. The solid thus obtained was recrystallized to give IIIg–l (Table 1).

(iii) Formation of IIIm, n : An equimolar (0.01 mol each) mixture of chalcone and I in abs. ethanol (100 ml) was refluxed for 1 hr. cooled. The separated product was filtered off and crystallized from the proper solvent to give IIIm,n (Table 1].

Basic Cyclization of IIIa-f : Formation of IVa–f

A suspension of IIIa–f (0.01 mol) in aq. NaOH (10%, 100 ml) was heated under reflux for 4 hrs. cooled, neutralized with dil. HCl and the resultant solid recrystallized to give IVa–f (Table 1); IR(IVc) : 3050 (aromatic CH), 2950 (aliphatic CH), 1680–1660 (C=O), 1580–1510 (C=O, C=N), 1480, 1440 (def. CH), 1010, 980 (phenyl groups), and 700 (C—Cl). UV (IVc) : 340 and 255. (IVd) : 340 and 260. PMR(IVc) : 4.3 (s, 2H, —CH=CH—), 7.3–7.7 (m, 14H, aromatic protons), (IVf); 1, 2, 1.8 (s, 3H 3H, CH_3, CH_3), 2.8–3.1 (s, 2H, —CH=CH—) and 7.3–7.7 (m, 14H, aromatic protons).

Cyclocondensation of IVc : Formation of Heterotricyclic System V

Compound IVc(0.01 mol), phenylhydrazine (0.01 mol) in abs. ethanol (50 ml) and piperidine (0.5 ml) was refluxed for 8 hrs. The reaction mixture was concentrated, cooled and poured onto ice HCl. The separated product was filtered, washed with cold water and crystallized to give V (Table 1). IR 3040 (aromatic CH), 2980 (aliphatic CH), 1600, 1550 (C=N) 1500–1440 (b, def. CH), 1000, 960, 850 (phenyl groups) and 700 (C—Cl). UV : 360 and 270.

Cycloaddition of III

(i) Formation of VI and VII : Compounds IIIc and or IIIi (1 g) in piperidine (1 ml) with ethanol (10 ml) was heated under refluxed for 6 hrs. cooled, and diluted. The solid obtained, filtered and crystallized to give VI

and or VII (Table 1). IR (VI) : 3500–3460 (OH), 3250 (NH) 3030 (aromatic CH), 2980–2940 (aliphatic CH), 1720–1690 (C=O), 1650–1580 (b, C=C, C=N), 1490, 1440 (def. CH), 1000, 960, 860 (phenyl groups) and 700 (C—Cl). UV (VI) : 335 and 260. PMR (VI) : 2.4–2.6 (m, 2H, CH_2), 4.1 (s, 1H, —CH=), 5.8 (s, 1H, OH) and 7.3–7.6 (m, 14H, aromatic protons).

Conversion of VI to VII

A suspension of VI (1 g) in aq. K_2CO_3 (10%, 100 ml) was warmed for 15 min, then cooled. The solid obtained on crystallization gave VII, m.pt. and m.m.pt. 197°.

(ii) Formation of VIIIa, b–A minture of IIIm and or IIIn (0.01 mol) in piperidine (0.5 ml) with abs. ethanol (50 ml) was refluxed for 6 hrs. then concentrated, cooled and diluted with HCl. The solid obtained was crystallized to give VIIIa and/or VIIIb (Table 1). IR : (VIIIb) : 3020 (aromatic CH), 2980 (aliphatic CH), 1620–1600 (C=N), 1500–1450 (def. CH), 1000, 900, 850 (phenyl groups) and 700, 640 (C—Cl).

Oxidation of VIIIb : Formation of 3-(3, 5-disubstituted pyrazolin-1-yl)-5, 6-diphenyl-1, 2, 4-triazine(IX)

A mixture of VIIIb (1 g) and $FeCl_3$ (10 ml) in ethanol (10 ml) was refluxed for 4 hrs. and diluted with cold water. The solid thus obtained crystallized to give IX (Table 1).

Reaction of IIIj with acrylonitrile : Formation of X

A mixture of IIIj (0.01 mol) and acrylonitrile (3 ml, in 3 ml water) in pyridine (30 ml) was heated under reflux for 3 hrs. cooled, then washed with dil. HCl. The solid obtained was crystallized to give X (Table 1); IR 3250 (NH), 3040 (aromatic CH), 2950 (aliphatic CH), 2250 (C=N), 1600 (C=C), 1510–1490, 1440 (def. CH), 1000, 950, 850 (phenyl groups) and 700 (C—Br).

Addition of maleic anhydride to IIIg, h : Formation of XIa, b

A mixture of IIIg and IIIh (0.01 mol) and maleic anhydride (0.01 mol) in dry benzene (100 ml) was refluxed for 12 hrs. then concentrated. The precipitated solid was filtered off and recrystallized from a proper solvent to give XIa, b (Table 1); IR (XIa) 3500-3150 (b, NH), 3020 (aromatic CH) 2980 (aliphatic CH), 1700, 1680 (C=O), 1650–1600 (C=C, C=N), 1500–1480 and 1450–1440 (def. CH), 1020, 920, 850 (phenyl groups). UV(Xb) : 275 and 260.

Reaction of IIIh with Br_2 : Formation of Dibromide Derivative XII

To a solution of Br_2 in $CHCl_3$ were added IIIh. The reaction mixture was stirred for 2 hrs. and the solvent was removed on a water bath. The solid thus obtained was crystallized to give XII (Table 1). IR(XII) : 3500–3100 (b, NH), 3040 (aromatic CH), 2960 (aliphatic CH), 1620, 1590 (C=C, C=N), 1490–1440 (def. CH), 1000, 950, 800 (phenyl groups) and 750, 700 (2 C—Br).

Action of phenylmagnesium bromide on IIIh : Formation of XIII

Compound IIIh (5 g) in dry benzene (100 ml) was added to the Grignard solution prepared from Mg (5 g), bromobenzene (30 ml) and freshly distilled and dry ether (100 ml), and the reaction mixture kept overnight at room temperature. The Grignard complex was decomposed with cold saturated aq. NH_4Cl solution. The organic layer was separated, dried (Na_2SO_4), filtered and solvent removed at room temperature. The solid obtained was crystallized to give XIII (Table 1): IR : 3200–3050 (b, NH, NH), 3020 (aromatic CH), 2950 (aliphatic CH), 1650 (C=C), 1440 (def. CH), 1050, 980 and 900 (phenyl groups). UV : 300. PMR : 4.1–4.3 (m, 2H, CH=CH), 7.2 (s, 1H, NH), 7.3–7.6 (m, 2 OH, aromatic protons), 15.5 (s, 1H, NH),

Acylation of IIIc, d : Formation of IIIo, p

A mixture of IIIc and or IIId (0.01 mol) and pivolyl chloride (0.01 mol) in DMF (10 ml) was warmed for 10 min., then poured onto ice HCl. The solid thus obtained was crystallized to give IIIo, p (Table 1).

Condensation of IIIo, p with hydrazine hydrate : Formation of hydrazones XIVa, b

A mixture of IIIo and IIIb (0.01 mol) and hydrazine hydrate (0.01 mol) in abs. ethanol (50 ml) was refluxed for 1 hr, cooled the solid obtained crystallized to give XIVa, b (Table 1).

Acidic cyclization of XIV : Formation of XV

A suspension of XIV (1 g) in conc. HCl (20 ml) was refluxed for 2 hrs, cooled. The solid obtained, washed with cold water and crystallized to give XV (Table 1); IR : 3010 (aromatic CH), 2900–2800 (aliphatic CH), 1730 (C=O), 1620 (C=N, C=C), 1500, 1430 (def. CH).

Reduction of IIIb, h and or IVb, h : Formation of XVI

As the same condition is reported[10]

TABLE 1

PHYSICAL DATA OF THE NEW PRODUCTS III-XV

Compound No.	Solvent	M.pt. [°C]	Yield (%)	Mol Formula*	Halogen analyses Calc./(Found)	
IIIa	Dil.DMF	98–100	30	$C_{20}H_{17}N_5O_2$		
IIIb	,,	195–196	50	$C_{25}H_{19}N_5O_2$		
IIIc	,,	210–212	75	$C_{25}H_{18}N_5ClO_2$	7.89	(7.00)
IIId	,,	149–150	70	$C_{25}H_{18}N_5BrO_2$	16.00	(15.20)
IIIe	,,	212–214	50	$C_{25}H_{19}N_5O_3$		
IIIf	Acetone	235–236	60	$C_{27}H_{24}N_6O_3$		
IIIg	Dil.DMF	210–211	50	$C_{19}H_{17}N_5$		
IIIh	,,	245–246	55	$C_{24}H_{19}N_5$		
IIIi	,,	191–192	65	$C_{24}H_{18}N_5Cl$	8.73	(7.85)
IIIj	Acetic acid	196–197	60	$C_{24}H_{18}N_5Br$	17.80	(16.90)
IIIk	Dil.DMF	174–175	60	$C_{24}H_{19}N_5O$		
III-l	,,	225–226	60	$C_{26}H_{24}N_6O$		
IIIm	Ethanol	75–76	85	$C_{31}H_{23}N_5Cl_2$	13.24	(12.30)
IIIn	Ethanol	65–66	70	$C_{31}H_{23}N_5Cl_2$	13.24	(12.25)
IIIo	Butanol	144–145	55	$C_{30}H_{26}N_5ClO_3$	6.66	(5.82)
IIIp	Dil.MeOH	95–97	50	$C_{30}H_{26}N_5BrO_3$	13.70	(13.50)
IVa	Dil.AcOH	209–210	45	$C_{20}H_{15}N_5O$		
IVb	,,	178–179	50	$C_{25}H_{17}N_5O$		
IVc	,,	248–250	65	$C_{25}H_{16}N_5ClO$	8.25	(7.35)
IVd	,,	202–203	60	$C_{25}H_{16}N_5BrO$	16.60	(15.80)
IVe	,,	204–205	55	$C_{25}H_{17}N_5O_2$		
IVf	Acetic acid	215–216	60	$C_{27}H_{22}N_6O$		
V	Acetic acid	147–150	50	$C_{31}H_{22}N_7Cl$	6.81	(5.95)
VI	Dil.AcOH	188–189	55	$C_{25}H_{18}N_5ClO_2$	7.90	(7.15)
VII	Dil.DMF	196–197	45	$C_{24}H_{18}N_5Cl$	8.73	(7.99)
VIIIa	Dil.EtOH	85–87	75	$C_{31}H_{23}N_5Cl_2$	13.24	(12.40)
VIIIb	Dil.EtOH	93–95	66	$C_{31}H_{25}N_5Cl_2$	13.24	(12.44)
IX	Acetic acid	69–70	35	$C_{31}H_{21}N_5Cl_2$	13.24	(12.55)
X	Acetic acid	255–256	65	$C_{27}H_{21}N_6Br$	15.70	(15.00)

TABLE 1 (Contd.)

Compound No.	Solvent	M.pt. [°C]	Yield (%)	Mol. Formula*	Halogen analyses Calcd./(Found)	
XIa	Benezene	197–199	60	$C_{25}H_{20}N_5O_3$		
XIb	Benezene	253–255	75	$C_{30}H_{22}N_5O_3$		
XII	Dil. MeOH	79–80	80	$C_{24}H_{19}N_5Br_2$	30.00	(29.63)
XIII	DMF	235–237	66	$C_{30}H_{25}N_5$		
XIVa	Dil. DMF	110–112	35	$C_{30}H_{28}N_7ClO_2$	6.50	(5.70)
XIVb	Dil. DMF	142–143	30	$C_{30}H_{28}N_7BrO_2$	13.37	(12.90)
XV	Ethanol	65–67	25	$C_{30}H_{25}N_6ClO$	6.9	(5.99)

*All the new products gave satisfactory C, H and N analyses.

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