1,2,4-Triazines. VI. Imidazo[1,2-*b*]-*as*-triazines (1)

I. Lalezari and Y. Levy

Department of Chemistry, Faculty of Pharmacy, University of Tehran, Iran

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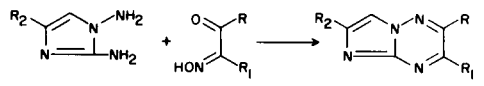
Imidazo[1,2-*b*]-*as*-triazines were obtained in high yields by heating substituted glyoxaldoximes with 1,2-diaminoimidazoles in the presence of hydrochloric acid. Phenylglyoxal hydrate in a similar reaction afforded a mixture of 2- and 3-diphenyl-6-arylimidazo[1,2-*b*]-*as*-triazines. α-Ketoacids and 1,2-diaminoimidazoles in the presence of hydrochloric acid afforded 2,6-disubstituted-4*H*-imidazo[1,2-*b*]-*as*-triazin-3-ones.

Base and acid-catalyzed cyclization of substituted glyoxaldoxime semicarbazones as well as the reaction of substituted glyoxaldoxime with thiosemicarbazide or aminoguanidine derivatives in acid or alkali mediums leading to *as*-triazine derivatives as described in our previous communications (2-6) prompted us to investigate the reaction of substituted glyoxaldoximes with 1,2-diaminoimidazoles. The reaction conducted in dilute hydrochloric acid, afforded high yields of imidazo[1,2-*b*]-*as*-triazines (**1a-h**) according to Scheme I.

SCHEME I

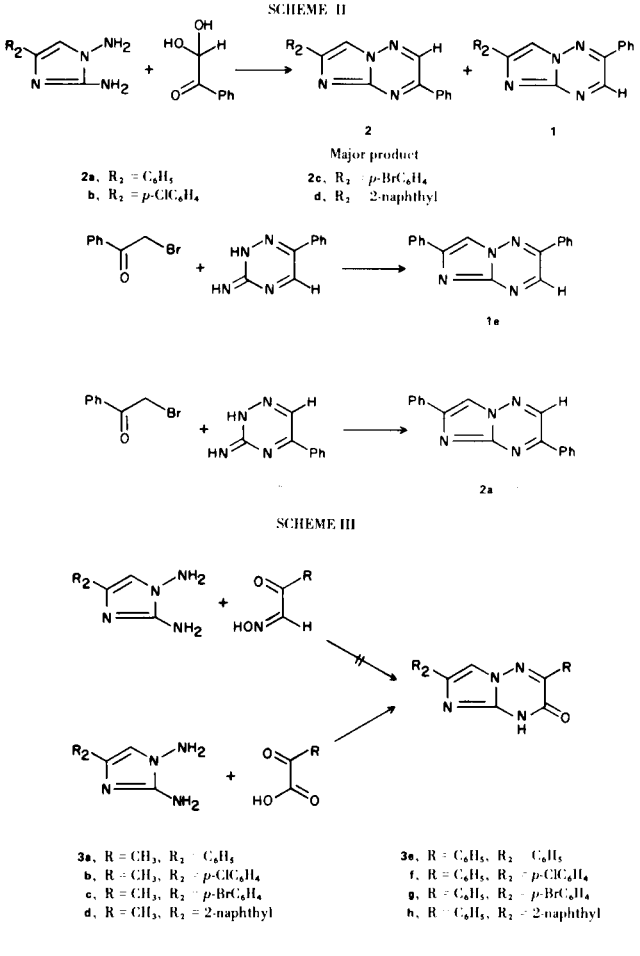


1a, R = R_1 = CH_3; R_2 = C_6H_5
b, R = R_1 = CH_3; R_2 = *p*-ClC_6H_4
c, R = R_1 = CH_3; R_2 = *p*-BrC_6H_4
d, R = R_1 = CH_3; R_2 = 2-naphthyl
1e, R = C_6H_5; R_1 = H; R_2 = C_6H_5
f, R = C_6H_5; R_1 = H; R_2 = *p*-ClC_6H_4
g, R = C_6H_5; R_1 = H; R_2 = *p*-BrC_6H_4
h, R = C_6H_5; R_1 = H; R_2 = 2-naphthyl

To ascertain the position of the phenyl group (R or R_1) in compounds **1e-h**, phenylglyoxal hydrate was allowed to react with the appropriate 1,2-diaminoimidazoles in acid solutions. The reaction product in each case was subjected to tlc. Two fractions were separated; the slow moving fraction (minor product) was identical with the products obtained by interaction of phenylglyoxaldoxime and corresponding 1,2-diaminoimidazoles and assigned as 2,6-diphenylimidazo[1,2-*b*]-*as*-triazines (**1e**). This compound was also identical with an authentic compound prepared according to the literature (7-9). The fast moving fraction was found to be 3-phenyl-6-arylimidazo[1,2-*b*]-*as*-triazine. 3,6-Diphenylimidazo[1,2-*b*]-*as*-triazine (**2a**) was compared with an authentic sample prepared by an independent method (8,9). (See Scheme II.)

Substituted glyoxaldoximes and 1,2-diaminoimidazoles in alkali solutions failed to give the expected 2,6-disubstituted-4*H*-imidazo[1,2-*b*]-*as*-triazin-3-ones (**3a-b**). However, these compounds were obtained by interactions of the appropriate α-keto acids and 1,2-diaminoimidazoles in acid medium. (See Scheme III.)

SCHEME II



2a, R_2 = C_6H_5
b, R_2 = *p*-ClC_6H_4
2c, R_2 = *p*-BrC_6H_4
d, R_2 = 2-naphthyl

SCHEME III

3a, R = CH_3, R_2 = C_6H_5
b, R = CH_3, R_2 = *p*-ClC_6H_4
c, R = CH_3, R_2 = *p*-BrC_6H_4
d, R = CH_3, R_2 = 2-naphthyl
3e, R = C_6H_5, R_2 = C_6H_5
f, R = C_6H_5, R_2 = *p*-ClC_6H_4
g, R = C_6H_5, R_2 = *p*-BrC_6H_4
h, R = C_6H_5, R_2 = 2-naphthyl

Infrared spectra of imidazo[1,2-*b*]-*as*-triazines could be used for identification and differentiation between the 2,6 and 3,6 diaryl compounds as well as 2,6-disubstituted-4*H*-imidazo[1,2-*b*]-*as*-triazin-3-ones. All of the 3,6-di-

arylimidazo[1,2-*b*]-*as*-triazines showed strong or medium intensity bands at 740-750 cm^{-1} while their 2,6-isomers and 2,3-dimethyl-6-aryl compounds did not show absorption in this region. 2,6-Disubstituted-4*H*-imidazo[1,2-*b*]-*as*-triazin-3-ones exhibited strong absorption bands at 1580-1590 cm^{-1}. Examination of the nmr spectra of the compounds prepared revealed that the 2*H* and 3*H* proton band appeared as a singlet at δ = 9.4 ± 0.1 ppm and 7*H* bands as a singlet at δ = 8.3 ± 0.2 ppm. 1,2-Diaminoimidazoles used in this work were prepared according to the literature (7). Data on the preparation, and properties of compounds prepared are given in Table I.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and were uncorrected. Ir spectra were obtained using a Leitz Model III spectrograph, as potassium bromide disks. Uv spectra were recorded on a Varian Techtron 635 spectrophotometer. Nmr spectra were taken using a Varian A60A instrument in deuteriochloroform-trifluoroacetic acid (90:10).

4-β-Naphthyl-1,2-diaminoimidazole.

1-Benzylidene-4-β-naphthyl-2-aminoimidazole was prepared by two hours refluxing of 2.4 g. (0.01 mole) 2-β-bromoacetylnaphthalene and 3.34 g. (0.02 mole) benzaldehyde guanylhydrazone in 20 ml. of ethanol. The precipitate obtained in this way was recrystallized from ethylengylcol monoethyl ether to give 66 per cent of light brown crystals, m.p. 253-255°. Hydrazinolysis (7) of the benzylidene derivative obtained failed to give the desired 1,2-diaminoimidazole. However, hydrolysis of the benzylidene derivative (5 g.) in 500 ml. of 1*N* hydrochloric acid and gradual removal of the benzaldehyde separated by distillation, a process which require eight days of heating, gave after neutralization with sodium hydroxide and crystallization in ethanol, 45 per cent of 4-β-naphthyl-1,2-diaminoimidazole m.p. 258-260°. Molecular weight by mass spectroscopy, m/e 224.

Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.64; H, 5.35. Found C, 69.53; H, 5.40.

All other 4-aryl-1,2-diaminoimidazoles were prepared according to the literature (7) and by the above modified procedure.

2,3-Dimethyl-6-phenylimidazo[1,2-*b*]-*as*-triazine (**1a**).

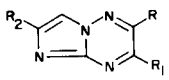
1,2-Diamino-4-phenylimidazole (7), 1.74 g. (0.01 mole) and 1 g. (0.01 mole) of diacetylmonoxime in 25 ml. of water containing 0.5 ml. of concentrated hydrochloric acid was refluxed for twelve hours. After cooling, the precipitate was filtered and crystallized from dioxane-water (50:50) to give 1.56 g. (70%) of **1a**; m.p. 219-220° (lit. (7) m.p. 218-220°). Molecular weight by mass spectroscopy, m/e 224; uv max (methanol): 371 nm; nmr: δ 2.31 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.23 (m, 5H, C_6H_5) and 8.2 (s, 1H, 7H) ppm; ir (potassium bromide): 3110, 1605, 1478, 1425, 1372, 1314, 1292, 1180, 1156, 1007, 916, 773, 745, 737 and 693 cm^{-1}.

Compounds **1b-1d** were prepared similarly (see Table I).

2,6-Diphenylimidazol[1,2-*b*]-*as*-triazine (**1e**).

A mixture of 1.84 g. (0.01 mole) 4-phenyl-1,2-diaminoimidazole (7) and 1.49 g. (0.01 mole) of phenylglyoxaldoxime in 30 ml. ethanol was refluxed for 1 hour. To the refluxing solution, 0.5 ml. of concentrated hydrochloric acid was added and

TABLE I



Compd. No.	R	R_1	R_2	M.P. °C	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found
1a	CH_3	CH_3	C_6H_5	219-220 (a)	72	$C_{13}H_{12}N_4$	69.64	69.76	5.35	5.40
1b	CH_3	CH_3	*p*-ClC_6H_4	250-252	62	$C_{13}H_{11}ClN_4$	60.34	60.33	4.25	4.31
1c	CH_3	CH_3	*p*-BrC_6H_4	267-270	71	$C_{13}H_{11}BrN_4$	51.48	51.53	3.67	3.72
1d	CH_3	CH_3	2-naphthyl	256-259	70	$C_{17}H_{14}N_4$	74.45	74.44	5.10	5.11
1e	C_6H_5	H	C_6H_5	228-230 (b)	48	$C_{17}H_{12}N_4$	75.00	75.09	4.41	4.44
1f	C_6H_5	H	*p*-ClC_6H_4	305-306	52	$C_{17}H_{11}ClN_4$	66.55	66.54	3.58	3.61
1g	C_6H_5	H	*p*-BrC_6H_4	307-308	31	$C_{17}H_{11}BrN_4$	58.11	58.14	3.13	3.09
1h	C_6H_5	H	2-naphthyl	258-259	59	$C_{21}H_{14}N_4$	78.26	78.48	4.34	4.29
2a	H	C_6H_5	C_6H_5	200-201	80	$C_{17}H_{12}N_4$	75.00	74.89	4.41	4.39
2b	H	C_6H_5	*p*-ClC_6H_4	252-253	83	$C_{17}H_{11}ClN_4$	66.55	66.68	3.58	3.63
2c	H	C_6H_5	*p*-BrC_6H_4	243-245	73	$C_{17}H_{11}BrN_4$	58.11	58.24	3.13	3.17
2d	H	C_6H_5	2-naphthyl	222-225	40	$C_{21}H_{14}N_4$	78.26	78.40	4.34	4.55
3a	CH_3	OH	C_6H_5	289-290	53	$C_{12}H_{10}N_4O$	63.71	63.81	4.42	4.41
3b	CH_3	OH	*p*-ClC_6H_4	311-313	51	$C_{12}H_9ClN_4O$	55.27	55.20	3.45	3.48
3c	CH_3	OH	*p*-BrC_6H_4	312-316	60	$C_{12}H_9BrN_4O$	47.21	47.30	2.95	3.12
3d	CH_3	OH	2-naphthyl	212-315	65	$C_{16}H_{12}N_4O$	69.56	69.55	4.34	4.29
3e	C_6H_5	OH	C_6H_5	310-312	90	$C_{17}H_{12}N_4O$	70.83	70.83	4.16	4.19
3f	C_6H_5	OH	*p*-ClC_6H_4	310-315	90	$C_{17}H_{11}ClN_4O$	63.25	63.31	3.41	3.39
3g	C_6H_5	OH	*p*-BrC_6H_4	321-323	62	$C_{17}H_{11}BrN_4O$	55.58	55.55	2.99	3.09
3h	C_6H_5	OH	2-naphthyl	317-322	83	$C_{21}H_{14}N_4O$	74.55	74.70	4.14	4.20

(a) Ref. (7) gives m.p. 218-220°. (b) Ref. (7) gives m.p. 220-222°.

the heating was continued four more hours. After cooling, the precipitate was separated and recrystallized from ethanol to give 0.72 g. (30%) of **1e** as a bright yellow crystalline powder, m.p. 228° (lit. (7) 220-222°). Molecular weight by mass spectroscopy, m/e 272; uv max (methanol): 394 and 248 nm; nmr: δ 7.73-8.15 (m, 10H, C_6H_5), 8.50 (s, 1H, 7H), 9.43 (s, H, 3H) ppm; ir: 3350, 1478, 1450, 1430, 1393, 1239, 1177, 1080, 1048, 1025, 956, 922, 903, 802, 765 and 691 cm^{-1}.

If the hydrochloric acid was added at the beginning of the reaction, a mixture of isomeric 2,6- and 3,6-diphenylimidazo-[1,2-*b*]-*as*-triazines, (**1e** and **2a**), was obtained which could be resolved by tlc on silica gel plates using chloroform as running solvent (see 3,6-diphenylimidazo[1,2-*b*]-*as*-triazines. Compounds **1f-h** were prepared similarly (see Table I).

3,6-Diphenylimidazo[1,2-*b*]-*as*-triazine (**2a**).

Method A.

To the hot solution of 1,84 g. (0.01 mole) 4-phenyl-1,2-diaminoimidazole (7) in 50 ml. of water containing 1 ml. of concentrated hydrochloric acid, 1.52 g. (0.01 mole) of phenylglyoxal hydrate was added and the reaction mixture was refluxed for 10 hours. After cooling, the bright yellow precipitate, 3.38 g. (88%), was dissolved in chloroform and subjected to preparative tlc using silica gel plate and chloroform as running solvent. Two fractions were separated, the slow moving fraction (*ca.*, 12%) was found to be pure **1e**. The fast moving fraction, after extraction from silica gel by boiling chloroform-ethanol mixture (75:25) and evaporation of the solvent, was recrystallized from chloroform to give 1.97 g. (80%) of **2a**, m.p. 200-201°. Molecular weight by mass spectroscopy, m/e 272; uv max (methanol): 407, 264 and 238 nm; nmr: 7.82-8.10 (m, 10H, C_6H_5), 8.47 (s, 1H, 7H), 9.50 (s, 1H, 2H); ir: 1462, 1232, 1175, 1158, 1072, 1047, 1018, 952, 923, 899, 887, 774, 763, 726 and 690 cm^{-1}.

Compounds **2b-d** were prepared similarly (see Table I).

Method B.

A mixture of 1.72 g. (0.01 mole) of 3-amino-5-phenyl-*as*-triazine and 1.99 g. (0.01 mole) of phenacylbromide in 25 ml. of ethanol was heated under reflux for 8 hours. The reaction mixture was dried under reduced pressure and the residue was recrystallized from chloroform to give 1 g. (37%) of **2a**, m.p. 200-201°.

2,6-Diphenyl-4*H*-imidazo[1,2-*b*]-*as*-triazin-4-one (**3a**).

A mixture of 1.84 g. (0.01 mole) of 4-phenyl-1,2-diaminoimidazole (7), 1.50 g. (0.01 mole) of phenylglyoxilic acid and 0.5 ml. concentrated hydrochloric acid in 30 ml. of water was refluxed for fourteen hours. After cooling, the precipitate was filtered and recrystallized from dioxane or dimethylsulfoxide to give 2.6 g. (90%) of **3e**, m.p. 310-312°. Molecular weight by mass spectroscopy m/e 288; uv max (methanol): 362 and 273 nm; nmr: δ 7.50-7.81 (m, 10H, C_6H_5), 8.20 (s, 1H, 7H) ppm; ir: 2930 1620, 1541, 1473, 1457, 1420, 1293, 1273, 1228, 1110, 1057, 1017, 935, 892, 870, 803, 785, 758, 724, 707 and 682 cm^{-1}.

Compounds **3a-h** were prepared similarly.

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REFERENCES

(1) For the previous papers see reference (6).

(2) I. Lalezari, *J. Org. Chem.*, 33, 4281 (1968).

(3) I. Lalezari, A. Shafiee and M. Yalpani, *Tetrahedron Letters*, 3059 (1969).

(4) I. Lalezari, N. Sharghi, A. Shafiee and M. Yalpani, *J. Heterocyclic Chem.*, 6, 403 (1969).

(5) I. Lalezari and H. Golgolab, *ibid.*, 7, 689 (1970).

(6) I. Lalezari, A. Shafiee and M. Yalpani, *ibid.*, 8, 689 (1971).

(7) H. Beyer, A. Hetzheim, H. Honeck, D. L. Ling and T. Pyl, *Chem. Ber.*, 101, 3151 (1968); A. Hetzheim, H. Pusch and H. Beyer, *ibid.*, 103, 3536 (1970).

(8) R. Fusco and S. Rossi, Italian patent, 536,121; *Chem. Abstr.*, 53 2264 (1959).

(9) L. M. Werbel and M. L. Zamora, *J. Heterocyclic Chem.*, 2, 287 (1965).