CONDENSATION OF 1,2-DIAMINOIMIDAZOLES WITH ISATINS

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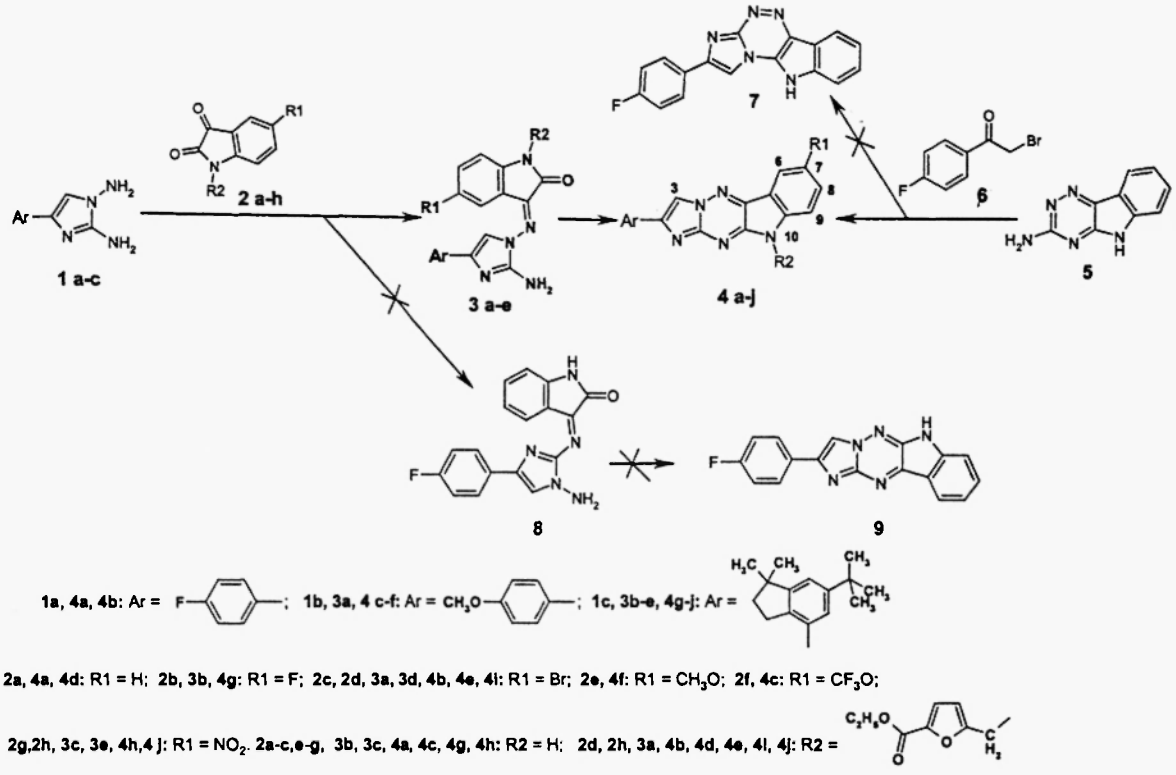
Abstract: Depending on the conditions, the reaction between 1,2-diaminoimidazoles **1** and isatin **2** yields 3-[(2-amino-4-aryl-1*H*-imidazol-1-yl)imino]-1,3-dihydro-2*H*-indol-2-ones **3** or 10*H*-imidazo[1',2':2,3]-1,2,4-triazino[5,6-*b*]indoles **4**. Compounds **3** were converted to products **4.**

Although the reaction of aromatic *ortho*-diamines with isatins has been studied previously,[1-14] little attention has been paid to the reactivity of *ortho*-diamines having nonequivalent amino groups. In particular, on the basis of limited experimental data, it has been suggested that the reaction of a 1,2-diaminoimidazole **1** (Ar = Ph) with isatin (**2a**) produces a fused tetracyclic product **4** (Ar = Ph, $R^1 = R^2 = H$).[15,16]



Since similar compounds are multidrug resistance modulators,[17] antiinflammatory drugs and cyclooxygenase type 2 inhibitors,[18] we studied condensation of 1,2-diaminoimidazoles **1** with isatins **2** in detail. It was found that in practical situations either 3-[(2-amino-4-aryl-1*H*-imidazol-1-yl)imino]-1,3-dihydro-2*H*-indol-2-ones **3** or 10*H*-imidazo[1',2':2,3]-1,2,4-triazino[5,6-*b*]indoles **4** are formed. Refluxing the starting materials **1** and **2** in trifluoroacetic acid leads to products **3** which, when refluxed in the medium of ethanol or acetic acid, or dry benzene containing a small amount of acetic acid, are converted into 4. If, however, the substrates **1** and **2** are allowed to react under the conditions of transformation of products **3** into products **4,** then immediately products **4** are formed. Better yields of 4, as high as 68%, were obtained when the reaction was run in dry benzene in the presence of acetic acid.

To validate the structure of compounds 4 a counter synthesis of **4a** by condensation of 3-amino-1,2,4-triazino[5,6-b]indole (**5**) with 4-fluorophenacyl bromide (**6**) was conducted. In so doing, we assumed that this reaction might yield two isomers, **4a** and **7.**

It was found that compound **4a** is formed in both cases. This conclusion was based on the analysis of the TLC and HPLC retention times, depression-free melting of the mixed sample, and the coincidence of IR spectra in the fingerprint region. The mass, NMR, UV and photoelectron spectra (Table) are fully consistent with the structure of compounds 4.

Isomeric compounds[19] and tautomers[20] can successfully be identified by quantum-chemical calculations combined with photoelectron spectroscopy. The Table shows experimental ionization potentials for isomers **4a**, **7**, and **9**, obtained from photoelectron spectra, and the values computed by the AMI semi-empirical method in the frames of Coupman's theorem.[21] It can be seen that the values of calculated ionization potentials IP_6 and IP_7 for isomers **4a, 7** and **9** differ noticeably. At the same time, for isomer **4a**, the computed ionization potential magnitudes IP_6 and IP_7 virtually coincide with those obtained experimentally. This finding provides additional support for the structure of compounds 4.

Table. Experimental and calculated ionization potentials (IP, eV) for compounds **4a**, **7** and **9**.

Isomers	IP_1	IP_2	IP_3	IP_4	IP_5	IP_6	IP_7	IP_8	IP_9	IP_{10}	IP_{11}
$\mathbf{4a}_{exper}$	7.74	8.33	9.14	9.27	9.50	**10.25**	**10.38**	10.93	11.45	11.64	
$\mathbf{4a}_{calcd}$	7.83	8.34	9.13	**9.21**	9.32	**10.19**	**10.38**	11.00	11.34	11.41	11.93
$\mathbf{7}_{calcd}$	8.13	8.23	8.94	9.45	9.55	**10.35**	**10.61**	11.05	11.36	11.48	11.77
$\mathbf{9}_{calcd}$	7.84	8.29	9.06	9.29	9.67	**9.93**	**10.20**	11.00	11.41	11.56	11.90

Compounds **3** show molecular ion peaks in their mass spectra, carbonyl absorptions at ν 1700-1710 cm^{-1} in the IR spectra, and primary amino group absorptions at δ 9.20-8.50 in the ^1H NMR

spectra. These data are consistent with isomers **3** and **8.** The structure of compounds **3** was established by their conversion into imidazotriazinoindoles **4** and by the counter synthesis of compound **4a.**

It should be noted that the presence of acceptor substituents at the indole moiety of compounds **3** considerably hampers their cyclization into compounds **4**. Thus, the cyclization of **3c** and **3e** takes 3 h while that of **3a, 3b,** and **3d** is completed in 30 min under similar conditions.

Experimental Section

Mass spectra were obtained on an API100 LS MS Perkin Elmer Sciex instrument. ^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer in DMSO-d_6 using TMS as an internal standard. IR spectra were measured on a 457 Perkin Elmer spectrometer in KBr tablets. Photoelectron spectra were recorded on a Perkin-Elmer PES-18 spectrometer and calibrated against xenon lines $2P_{1/2}$ and $2P_{3/2}$ at 12.13 and 13.43 eV. The quantum-chemical calculations by the AMI semi-empirical procedure were done using the MOPAC[20] software package. The geometry was optimized by means of MM^+ molecular mechanics technique.

General Procedure for the synthesis of 3-[(2-amino-4-aryl-1H-imidazol-1-yl)imino]-1,3-dihydro-2H-indol-2-ones **3**. To 10 ml of trifluoroacetic acid, 0.001 mol of 1,2-diaminoimidazole **1** and 0.001 mol of isatin **2** was added. The mixture was heated under reflux for 2 h and concentrated, and the residue was dissolved in chloroform. The solution was chromatographed on silica gel using an acetone-chloroform mixture (1:10) as eluent.

3-{[2-Amino-4-(4-methoxyphenyl)-1H-imidazol-1-yl]imino}-5-bromo-1-(5-ethoxycarbonylfuryl-2-methyl)-1,3-dihydro-2H-indol-2-one (**3a**): yield 48%; m.p. 235-237 °C; MS m/z 564; IR 1700 cm^{-1}; ^{1}H NMR δ 8.75 (1H, s), 8.5 (2H, bs), 8.3 (1H, d, J = 1.0 Hz), 7.6 (2H, d, J = 8.4 Hz), 7.55 (1H, d, J = 8.2 Hz), 7.35 (2H, m), 7.0 (2H, d, J = 8.4 Hz), 6.65 (1H, d, J = 3.5 Hz), 5.05 (2H, s) 4.25 (2H, q, J = 6.9 Hz) 3.85 (3H, s), 1.30 (3H, t, J = 6.9 Hz).

3-{[2-Amino-4-(1,1-dimethyl-6-tert-butylindan-4-yl)-1H-imidazol-1-yl]imino -1,3-dihydro-5-fluoro -2H-indol-2-one (**3b**): yield 35%; m.p. >350 °C; MS m/z 446; IR 1705 cm^{-1}; ^{1}H NMR δ 11.1 (1H, s), 9.2 (2H, bs) 8.9 (1H, s), 7.95 (1H, m), 7.65 (1H, d), 7.1 (1H, m), 7.05 (1H, d), 6.85 (1H, m), 2.9 (2H, t, J = 8.8 Hz), 2.05 (2H, t, J = 8.8Hz), 1.35 (9H, s), 1.25 (6H, bs).

3-{[2-Amino-4-(1,1-dimethyl-6-tert-butylindan-4-yl)-1H-imidazol-1-yl]imino}-1,3-dihydro-5-nitro-2H-indol-2-one (**3c**): yield 68%; m.p. >350 °C; MS m/z 467; IR 1705 cm^{-1}; ^{1}H NMR δ 11.6 (1H, s), 9.1 (2H, bs) 8.9 (2H, m), 8.2 (1H, d), 7.6 (1H, d), 7.2 (1H, d), 2.95 (2H, t, J = 8.8 Hz), 2.35(3H, s), 2.0 (2H, t, J = 8.8 Hz), 1.35 (9H, s), 1.25 (6H, bs).

3-{[2-Amino-4-(1,1-dimethyl-6-tert-butylindan-4-yl)-1H-imidazol-1-yl]imino}-5-bromo-1,3-dihydro-2H-indol-2-one (**3d**): yield 35%; m.p. 218-220 °C; MS m/z 660; IR 1710 cm^{-1}; ^1H NMR δ 9.15 (2H, bs), 8.8 (1H, s), 8.45 (1H, d), 7.6 (1H, d), 7.55 (1H, m), 7.35 (3H, m), 6.7 (1H, d, J = 3.5 Hz), 5.1 (2H, s), 4.3 (2H, q, J = 7.0 Hz) 2.95 (2H, t, J = 8.8 Hz), 2.0 (2H, t, J = 8.8 Hz), 1.35 (9H, s) 1.2 (9H, bs).

3-{[2-Amino-4-(1,1-dimethyl-6-tert-butylindan-4-yl)-1H-imidazol-1-yl]imino}-1,3-dihydro-5-nitro-2H-indol-2-one (**3e**): yield 43%; m.p. 210-212 °C; MS m/z 626; IR 1700 cm^{-1}; ^1H NMR δ 9.15 (2H bs) , 9.05 (1H, d), 8.85 (1H, s), 8.40 (1H, m), 7.6 (1H, d), 7.6 (1H, m), 7.35 (2H, m), 6.75 (1H, d, J = 3.5 Hz), 5.1 (2H, s) 4.3 (2H, q), 2.95 (2H, t, J = 8.8 Hz), 2.0 (2H, t, J = 8.8 Hz), 1.35 (9H, s), 1.2 (9H, bs).

Procedures for the synthesis of 10H-imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indoles **4.** *Method A.* A mixture consisting of 10 ml of dry benzene, 0.3 ml of and 3% acetic acid, 0.001 mol of 1,2-diaminoimidazole **1** and 0.001 mol of isatin **2** was heated under reflux for 3 h and then cooled, and the resulting precipitate was filtered off and washed by refluxing in acetone. The product 4 was dried at 70 °C. *Method B.* A mixture consisting of 15 ml of dry benzene, 2 ml of acetic acid, and 50 mg of compound **3** was heated under reflux for 0.5 to 3 h and then cooled. The precipitate was filtered off and washed on a filter with hot ethanol, and then dried at 70 °C. *Method C* for *2-(4-fluorophenyl)-10H-imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole* (**4a**). A solution of 0.28 g (1.5 mmol) of 3-amino-1,2,3-triazino[5,6-*b*]indole **5**[16] and 0.42 g (1.5 mmol) of ω-bromo-4-fluoroacetophenone (6) in 10 ml of DMF was heated under reflux for 1 h. The resulting precipitate was filtered off, washed on a filter with acetone and dried at 70 °C.

Yield (%) - method - reaction time (min). **4a**: 89-A-30, 68-B-30, 64-C-60; m.p. >350 °C; MS m/z 305; ^1H NMR δ 12.0 (1H, s), 8.6 (1H, s), 8.2 (1H, d, J = 8.3 Hz), 8.0 (2H, m), 7.75 (1H, m), 7.5 (1H, d, J = 8.3 Hz), 7.35 (1H, m) 7.25 (2H, m).

7-Bromo-10-(5-ethoxycarbonylfuryl-2-methyl)-2-(4-fluorophenyl)imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4b**): 45-B-30; m.p. 210-212 °C; MS m/z 535; ^1H NMR δ 8.6 (1H, s), 8.25 (1H, d, J = 1.0 Hz), 8.00 (2H, m), 7.75 (1H, m), 7.7 (1H, d, J = 8.2 Hz), 7.25 (3H, m), 6.65 (1H, d, J = 3.5 Hz), 5.65 (2H, s), 4.2 (2H, q, J = 7.0 Hz), 1.25 (3H, t, J = 7.0 Hz).

2-(4-Methoxyphenyl)- 7-trifluoromethoxy-10H-imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4c**): 53-B-30; m.p. >350 °C; MS m/z 535; ^1H NMR δ 12.25 (1H, s), 8.5 (1H, s), 8.1 (1H, d, J = 1.0 Hz), 8.0 (2H, d, J = 8.4 Hz), 7.5 (2H, m), 7.0 (2H, d, J = 8.4 Hz), 3.85 (3H, s). *10-(5-Ethoxycarbonylfuryl-2-methyl)-2-(5-methoxyphenyl)imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole* (**4d**): 40-B-30; m.p. 215-216 °C; MS m/z 449; ^1H NMR δ 8.55 (1H, s), 8.2 (1H, d, J = 8.1 Hz), 7.95

(2H, d, J = 8.4 Hz), 7.7 (2H, m), 7.35 (1H, t, J = 8.1 Hz), 6.95 (2H, d, J = 8.4 Hz), 7.15 (1H, d, J = 3.5 Hz), 6.65 (1H, d, J = 3.5 Hz), 5.65 (2H, s), 4.20 (2H, q, J = 7.0 Hz), 3.85 (3H, s), 1.25 (3H, t, J = 7.0 Hz).

7-Bromo-10-(2-ethoxycarbonylfuryl-2-methyl)-2-(4-methoxyphenyl)imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4e**): 85-A-90; m.p. 250-251 °C; MS m/z 564; ^{1}H NMR δ 8.65 (1H, s), 8.25 (1H, d, J = 1.0 Hz), 8.0 (2H, m), 7.75 (1H, m), 7.7 (1H, d), 7.25 (3H, m), 6.7 (1H, d, J = 3.5 Hz), 5.65 (2H, s), 4.2 (2H, q, J = 7.0 Hz), 3.75 (3H, s), 1.25 (3H, t, J = 7.0 Hz).

7-Methoxy-2-(4-methoxyphenyl)-10H-imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4f**): 27-B-30; m.p. 338-340 °C; MS m/z 347; ^{1}H NMR δ 11.85 (1H, s), 8.5 (1H, s), 8.0 (2H, d, J = 8.4 Hz), 7.65 (1H, d, J = 1.0 Hz), 7.5 (2H, m), 7.0 (2H, d, J = 8.4 Hz), 3.85 (3H, s).

2-(1,1-Dimethyl-6-tert-butylindan-4-yl)- 7-floro-10H-imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4g**): 93-A-30, 54-B-30; m.p. >350 °C; MS m/z 447; ^{1}H NMR δ 12.2 (1H, s), 8.40 (1H, s), 8.15 (1H, d), 7.9 (1H, d, J = 1.0 Hz), 7.4 (2H, m), 7.15 (1H, d), 3.2 (2H, t, J = 8.8 Hz), 2.05 (2H, t, J = 8.8 Hz), 1.4 (15H, bs).

2-(1,1-Dimethyl-6-tert-butylindan-4-yl)- 7-nitro-10H-imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4h**): 63-A-150; m.p. >350 °C; MS m/z 469; ^{1}H NMR δ 11.9 (1H, s) 8.6 (1H, s), 8.1 (1H, d), 7.95 (1H, d), 7.5 (1H, d), 7.2 (1H, d), 2.25 (3H, s), 3.2 (2H, t, J = 8.7 Hz), 2.05 (2H, t, J = 8.7 Hz), 1.4 (15H, bs).

7-Bromo-10-(5-ethoxycarbonylfuryl-2-methyl-2-(1,1-dimethyl-6-tert-butylindan-4-yl)imidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4i**): 87.5-A-90; m.p. 173-174 °C; MS m/z 642; ^{1}H NMR δ 8.45 (1H, s), 8.35 (2H, m), 7.75 (2H, m), 7.2 (2H, m), 6.75 (1H, d, J = 3.5 Hz) 5.8 (2H, s), 4.25 (2H, q, J = 7.0 Hz), 3.15 (2H, t, J = 8.8 Hz), 2.05 (2H, t, J = 8.8 Hz), 1.4 (9H, s), 1.3 (9H, bs).

10-(5-Ethoxycarbonylfuryl-2-methyl)-2-(1,1-dimethyl-6-tert-butylindan-4-yl)-7-nitroimidazo[1',2':2,3]-1,2,4-triazino[5,6-b]indole (**4j**): 80.5-A-180, 40-B-180; m.p. 250-251 °C; MS m/z 608; ^{1}H NMR δ 8.4 (1H, s), 8.15 (1H, d), 7.9 (1H, d, J = 1.0 Hz), 7.4 (2H, m), 7.15 (2H, m), 6.7 (1H, d, J = 3.5 Hz) 3.2 (2H, t, J = 8.8 Hz), 2.05 (2H, t, J = 8.8 Hz), 1.4 (15H, bs).

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