Reaction of 2-Aminobenzohydrazides with Schiff Bases. A New Route to 3-Benzylideneamino-4(3*H*)-quinazolinones and 2-[2-(Methylamino)-phenyl]-5-aryl-1,3,4-oxadiazoles

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Reaction of 2-aminobenzohydrazides with Schiff bases in methanol followed by $KMnO_4$ oxidation has resulted in the respective formation of 3-benzylideneamino-4(3*H*)-quinazolinones and 2-[2-(methylamino)-phenyl]-5-aryl-1,3,4-oxadiazoles, characterized by spectral and analytical methods.

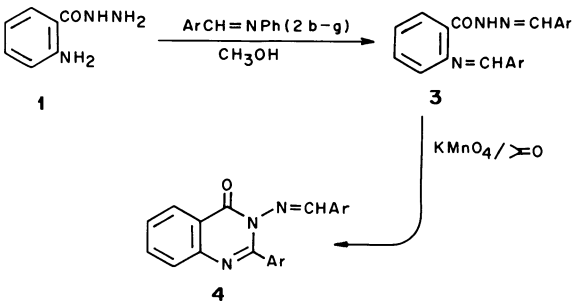
We have recently reported a facile one-step synthesis of 3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones, the aza analogues of pharmacologically important 1,4-benzodiazepines, from isatoic anhydride and aroylhydrazines.[1] But the product yields in this reaction were moderate (30—50%) and the work-up involved extensive chromatography. We surmised that cyclization of 2-aminobenzohydrazide (**1**) by insertion of a carbon between the terminal nitrogens would provide a direct route to triazepin-5-ones. Schiff bases are known to participate in heterocyclization reactions acting as a source of carbon, sometimes more effectively than the corresponding carbonyl compounds.[2] Hence the reactions of 2-amino- and 2-(methylamino)benzohydrazides with *N*-benzylideneanilines were carried out and the results are discussed here.

Results and Discussion

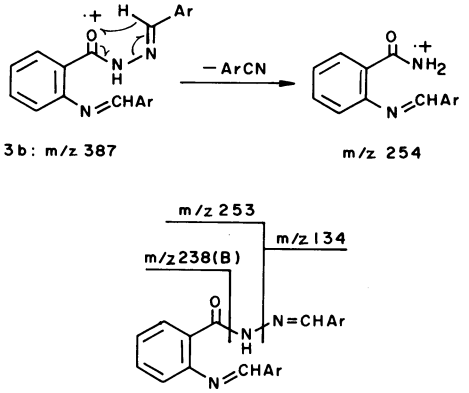
2-Aminobenzohydrazide (**1**) reacts with *N*-(4-methoxybenzylidene)aniline (**2b**) in methanol at ambient temperature, to give a colorless crystalline product, mp 221 °C, whose elemental analysis and molecular weight (M^+ at *m/z* 387) tallies with the molecular formula $C_{23}H_{21}N_3O_3$, formally derived from one mole of **1** and two moles of the Schiff base. The same product was formed irrespective of the stoichiometry of reaction. The infrared (KBr, ν_{NH} 3280, $\nu_{C=O}$ 1660, $\nu_{C=N}$ 1610 cm^{-1}) and ^1H NMR (DMSO-d_6) spectra suggested *N*-[2-(4-methoxybenzylideneamino)benzoyl]-*N'*-(4-methoxybenzylidene)hydrazine (**3b**) structure for the product. The two azomethine protons could be discerned in ^1H NMR spectrum by the chemical shift values at δ 8.9 and 8.95. The hydrazone structure, **3b** was preferred also by its fragmentation behavior under electron impact which is characteristic of aroylhydrazones.[3] The mass spectrum of **3b** thus showed intense fragmentation peaks formed by N–N bond fission and α-cleavage reactions of the molecular ion.

Attempts to cyclize **3b** to the triazepinone by permanganate oxidation gave a product **4b**, mp 185 °C, whose molecular weight (M^+ at *m/z* 385). indicated loss of two hydrogens from **3b**. However, the spectral data is more in confirmity with 3-benzylideneamino-2-aryl-4-(3*H*)-quinazolinone structure. The IR spectrum is devoid of NH absorptions, and the carbonyl peak at 1680 cm^{-1} is similar to that of 3-substituted 4(3*H*)-quinazolinone.[4] The ^1H NMR showed the presence of only one azomethine proton (at δ 8.6) and successive loss of two 4-methoxybenzonitrile moieties from the molecular ion was indicated in the mass spectrum.

The reaction of **1** with Schiff bases has been extended to six other benzylideneanilines (**2a—g**) and good yields of the corresponding *N*-[2-(4-substituted benzylideneamino)benzoyl]-*N'*-(4-substituted benzylidene)hydrazines (**3**) were isolated except in the case of *N*-benzylideneaniline (**2a**). **3** was oxidized with permanganate to give quantitative yields of 3-benzylideneamino-4(3*H*)-quinazolinones, providing a



Scheme 1.



Scheme 2. Mass spectral fragmentation of product, **3b**.

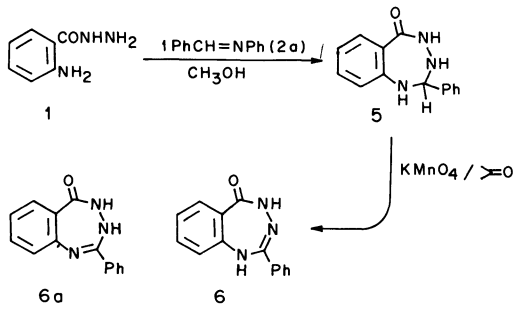
new route for the synthesis of **4**.

The reaction of **1** with **2a** proceeded in a different way and gave a product, mp 190 °C whose M^+ (*m/z* 239) in the mass spectrum indicated it to be a 1:1 product. The electronic λ_{max} (log ε) [206 (3.63), 219 (3.90), 252 (3.70), 292 (4.05), 303 (2.97), 341 (3.10)] and IR spectra (ν_{NH} 3280, $\nu_{C=O}$ 1670 cm^{-1}) are consistent with 2-phenyl-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-5-one (**5**) structure. Compound **5** was found not soluble in benzene, chloroform, dimethyl sulfoxide, and acetone in such concentrations for obtaining a good continuous sweep ^1H NMR spectrum. **5** on permanganate oxidation, or on reaction with one mole of *N*-benzylideneaniline in methanol, gave a product **6**, mp 152 °C. The mass spectrum of **6** (M^+ at *m/z* 237) showed it to be a dehydrogenated product of **5** and the appearance of a peak at 1610 cm^{-1} (C=N) in addition to 1670 cm^{-1} (C=O) corroborates the assumption. Based on these data **6** was assigned 2-phenyl-1,4-dihydro-5*H*-1,3-4-benzotriazepin-5-one structure. **6** was also formed in the 1:2 molar reaction of **1** and **2a**.

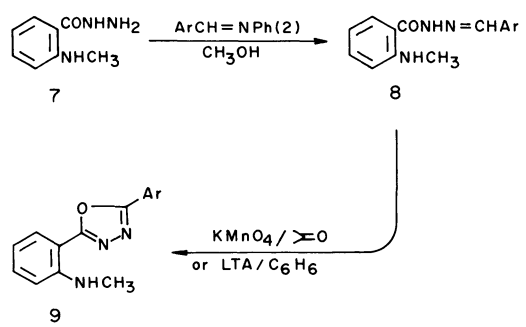
The product **6** is an isomer of **6a** (mp 179 °C)[1] which may be formally derived from proton transfer. However, attempts to convert **6** to **6a** (or vice versa) by 4 M HCl (1 M=1 mol dm^{-3}) did not succeed. Hence, the structures of **5** and **6** were tentatively assigned on the basis of spectral data.

The reason why the reaction of **1** with **2a** gives **5** instead of **3a** is not clear.

To prevent the possibility of diarylidene compounds, 2-(methylamino)benzohydrazide (**7**) was reacted with *N*-benzylideneanilines. An equimolar mixture of **7** and **2b** in methanol gave a colorless crystalline product, mp 176 °C at room temperature, whose structure was confirmed as *N*-[2-(methylamino)benzoyl]-*N'*-(4-methoxybenzylidene)hydrazine (**8b**) from its mass (M^+ 283) and IR spectra (ν_{NH} 3240 $\nu_{C=O}$ 1670 cm^{-1}). The permanganate oxidation of **8b** gave a product which showed the molecular ion at *m/z* 281, two amu less than the starting **8b**. Surprisingly the IR (ν_{NH} 3190, $\nu_{C=N}$ 1600 cm^{-1}] was devoid of carbonyl absorption suggesting 2-[2-(methylamino)phenyl]-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**9b**) structure. The carbonyl group absorbs around 1670 cm^{-1} in a triazepinone,[1] whose formation is possible in this oxidation reaction. **9b** was also obtained when the oxidation was carried out using lead tetraacetate (LTA). Synthesis of 1,3,4-oxadiazoles by oxidative cyclization of *N*-benzoylhydrazones or semicarbazones of aldehydes has been reported.[5] The reaction of **7** and five other *N*-benzylideneanilines afforded corresponding hydrazones, (**8a—f**). **8** Underwent both permanganate and LTA oxidation reactions to give good yields of **9**. Further evidence for the assigned structure of **9** was provided by comparison with authentic samples.[6] Formation of **9** from **8** is likely to proceed through the intermediacy of an enol form and the preference for oxadiazole ring is due to its thermodynamic stability and steric implications of methylamino group in the cyclization step.



Scheme 3.



Scheme 4.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord 337 spectrophotometer, ^1H NMR spectra on Varian A-60D instrument using TMS as internal standard and mass spectra on a Perkin-Elmer Hitachi RMU-6L instrument.

***N*-[2-(Benzylideneamino)benzoyl]-*N'*-benzylidene)hydrazines (3). General Procedure:** 2-Aminobenzohydrazide (**1**, 1 mmol) was dissolved in methanol (5 ml) and *N*-benzylideneaniline (**2**, 1 mmol) was added to it with thorough shaking and the mixture left aside for few minutes at room temperature. **3** Separated out from the clear solution, filtered and recrystallized from suitable solvent (Table 1).

3-Benzylideneamino-2-aryl-4-(3*H*)-quinazolinones (4). General Procedure: *N*-[2-(Benzylideneamino)benzoyl]-*N'*-benzylidenehydrazine (**3**, 10 mmol) was dissolved in dry acetone (100 ml) and $KMnO_4$ (1 gram) was added to it. The mixture was refluxed on water bath and further quantities of $KMnO_4$ were added to the boiling solution until pink color persisted. The solution was filtered and acetone was distilled off from the filtrate. The residue thus obtained was taken in water (25 ml) and excess $KMnO_4$ was destroyed with sodium sulfite solution (15 ml). The solution was extracted with chloroform (3×50 ml). The chloroform extract was dried over anhydrous sodium sulfate and the solvent was distilled off to yield crude product, **4**

Table 1. Characterisation Data of *N*-[2-(Benzylideneamino)benzoyl]-*N'*-benzylidenehydrazines (**3**), 3-Benzylideneamino-2-aryl-4(3*H*)-quinazolinones (**4**) and *N*-[2-(Methylamino)benzoyl]-*N'*-benzylidenehydrazines (**8**)

Compd	Ar	Mp (θ_m/°C)	Yield %	UV(MeOH) λ_{max}/nm (log ε)	IR(KBr) cm^{-1} NH	C=O	C=N	^{1}H NMR(δ)	Molecular formula		Calcd (%)	Found (%)
3b	4-$MeOC_6H_4$	221 (C_2H_5OH)	70	224 (3.17) 261 (3.26) 303 (3.33)	3280	1660	1610	3.9(s, 6H, -2OCH_3) 5.5(1H, NH) 7.9(m, 12H, aromatic) 8.9(s, 1H, azomethine) 8.95(s, 1H, azomethine)	$C_{23}H_{21}N_3O_3$	C H N	71.31 5.42 10.85	71.58 5.47 10.73
3c	4-MeC_6H_4	185 (C_6H_6)	68	226 (3.18) 257 (3.34) 305 (3.41)	3300	1660	1610	2.3(s, 6H, -2CH_3) 7.8(m, 12H, aromatic) 8.8(s, 1H) 8.85(s, 1H, azomethine)	$C_{23}H_{21}N_3O$	C H N	77.74 5.91 11.83	77.63 5.85 11.92
3d	4-$Me_2NC_6H_4$	238 (C_6H_6)	72	205 (3.14) 220 (3.16) 265 (3.42) 347 (3.28)	3250	1660	1610	3.3(m, 12H, 2NMe_2) 8.0(m, 12H aromatic) 8.8(s, 1H) 8.84(s, 1H, azomethine)	$C_{25}H_{27}N_5O$	C H N	72.63 6.53 16.94	72.46 6.58 16.90
3e	4-ClC_6H_4	159 (C_6H_6/ C_2H_5OH)	73	224 (3.19) 253 (3.33) 295 (3.42) 308 (3.43) 340 (3.28)	3270	1660	1610	—	$C_{21}H_{15}N_3OCl_2$	C H N	63.63 3.78 10.60	63.42 3.83 10.49
3f	4-$NO_2C_6H_4$	234 (CH_3OH)	70	229 (3.20) 258 (3.27) 297 (3.34) 310 (3.41)	3280	1660	1610	7.9(m, 12H, aromatic) 5.1(s, 1H, NH) 8.9(s, 1H) 8.95(s, 1H)	$C_{21}H_{15}N_5O_5$	C H N	60.43 3.59 16.78	60.57 3.63 16.70
3g	2-ClC_6H_4	203 (pet. ether/ C_6H_6)	69	206 (3.18) 226 (3.32) 260 (3.41) 305 (3.41)	3250	1660	1610	—	$C_{21}H_{15}N_3OCl_2$	C H N	63.63 3.78 10.60	63.51 3.87 10.56
4b	4-$MeOC_6H_4$	185 (C_6H_6)	80	228 (3.54) 248 (3.59) 281 (3.62) 326 (3.74)	—	1680	1600	3.9(s, 6H, -2OCH_3) 7.9(m, 12H aromatic) 8.9(s, 1H)	$C_{23}H_{19}N_3O_3$	C H N	71.68 4.93 10.90	71.81 4.88 10.78
4c	4-MeC_6H_4	145 (C_2H_5OH)	82	225 (3.51) 253 (3.62) 284 (3.70) 324 (3.74)	—	1680	1600	2.3(s, 6H, -2CH_3) 7.8(m, 12H aromatic) 8.8(s, 1H)	$C_{23}H_{19}N_3O$	C H N	78.18 5.38 11.89	78.30 5.42 11.93

4d	4-$Me_2NC_6H_4$	204 (pet. ether/ C_6H_6)	78	222 (3.53) 261 (3.63) 277 (3.68) 352 (3.79)	—	1680	1600	3.3(m, 12H, $-2NMe_2$) 7.9(m, 12H, aromatic) 8.9(s, 1H)	$C_{25}H_{25}N_5O$	C H N	72.99 72.76 6.08 6.02 17.03 17.10
4e	4-ClC_6H_4	225 (C_6H_6)	82	228 (3.50) 255 (3.59) 280 (3.71) 342 (3.69)	—	1680	1600	—	$C_{21}H_{13}N_3OCl_2$	C H N	63.95 63.87 3.29 3.33 10.65 10.62
4f	4-$NO_2C_6H_4$	198 (C_2H_5OH)	78	235 (3.53) 250 (3.58) 273 (3.73) 317 (3.66)	—	1680	1600	—	$C_{21}H_{13}N_5O_5$	C H N	60.72 60.56 3.13 3.16 16.86 16.78
4g	2-ClC_6H_4	176 (C_6H_6)	80	212 (3.51) 258 (3.63) 282 (3.61) 313 (3.74)	—	1680	1600	7.8(m, 12H, aromatic) 8.8(s, 1H)	$C_{21}H_{13}N_3OCl_2$	C H N	63.95 64.07 3.29 3.22 10.65 10.60
8a	C_6H_5	192 (pet. ether/ C_6H_6)	82	220 (4.29) 257 (4.27) 362 (4.36)	3270	1670	1605	—	$C_{15}H_{15}N_3O$	C H N	71.14 70.96 5.92 5.86 16.60 16.63
8b	4-$MeOC_6H_4$	176 (C_6H_6)	82	212 (4.21) 224 (4.21) 263 (4.39) 358 (4.42)	3240	1670	1605	—	$C_{16}H_{17}N_3O_2$	C H N	67.84 67.78 6.00 5.95 14.84 14.88
8c	4-MeC_6H_4	212 (C_2H_5OH)	80	217 (4.25) 258 (4.31) 349 (4.19)	3280	1670	1605	—	$C_{16}H_{17}N_3O$	C H N	71.91 71.64 6.36 6.47 15.73 15.68
8d	4-$Me_2NC_6H_4$	171 (pet. ether)	83	215 (4.19) 226 (4.33) 264 (4.27) 368 (4.43)	3250	1670	1605	—	$C_{17}H_{20}N_4O$	C H N	68.91 69.06 6.75 6.79 18.91 18.86
8e	4-ClC_6H_4	231 (C_6H_6)	85	220 (4.22) 252 (4.36) 297 (4.38) 360 (4.43)	3300	1670	1605	—	$C_{15}H_{14}N_3OCl$	C H N	62.71 62.53 4.87 4.83 14.63 14.65
8f	4-$NO_2C_6H_4$	236 (C_2H_5OH)	83	224 (4.21) 253 (4.31) 310 (4.29) 372 (4.38)	3280	1670	1605	—	$C_{15}H_{14}N_4O_3$	C H N	60.40 60.53 4.69 4.66 18.79 18.69

Table 2. Characterization Data of 2-[2-(Methylamino)phenyl]-5-aryl-1,3,4-ozadiaxoles (**9**)

Compd	Ar	Mp θ_m/°C	Yield with $KMnO_4$ %	Yield with LTA %	UV(MeOH) λ_{max}/nm (log ε)	Molecular formula		Calcd (%)	Found (%)
9a	C_6H_5	142 (pet. ether)	85	66	253 (4.62) 272 (4.71) 280 (4.78) 293 (4.83) 375 (4.74)	$C_{15}H_{13}N_3O$	C H N	71.71 5.17 16.73	71.56 5.14 16.79
9b	4-$MeOC_6H_4$	143 (C_6H_6)	83	65	212 (4.56) 235 (4.67) 260 (4.89) 280 (4.68) 288 (4.77) 300 (4.76)	$C_{16}H_{15}N_3O_2$	C H N	68.32 5.33 14.94	68.51 5.35 14.88
9c	4-MeC_6H_4	125 (C_6H_6)	83	60	—	$C_{16}H_{17}N_3O$	C H N	71.91 6.36 15.73	71.79 6.39 15.71
9d	4-$Me_2NC_6H_4$	129 (C_2H_5OH)	82	61	—	$C_{17}H_{18}N_4O$	C H N	69.38 6.12 19.04	69.22 6.09 19.09
9e	4-ClC_6H_4	132 (pet. ether/ C_6H_6)	84	60	—	$C_{15}H_{12}N_3OCl$	C H N	63.04 4.20 14.71	62.89 4.23 14.69
9f	4-$NO_2C_6H_4$	210 (C_6H_6)	80	64	240 (4.65) 295 (4.82) 391 (4.76)	$C_{15}H_{12}N_4O_3$	C H N	60.81 4.05 18.91	61.06 4.07 18.84

IR (KBr) spectrum of all these compounds showed NH absorption around 3200 cm^{-1}; C=N absorption at 1600 cm^{-1}.

which was recrystallized from suitable solvent (Table 1).

2-Phenyl-1,2,3,4-tetrahydro-5*H*-1,3,4-benzotriazepin-5-one (5). 2-Aminobenzohydrazide (**1**, 0.15 g) was dissolved in methanol (6 ml) and *N*-benzylideneaniline (**2a**, 0.18 g) was added to it with thorough shaking and the mixture left aside for few minutes at room temperature. White-colored compound (**5**) that separated from the solution was filtered and recrystallized from benzene (mp 190 °C yield 76%).

Found: C, 70.44; H 5.41; N 17.45%. Calcd for: C, 70.30; H, 5.44; N, 17.57%.

2-Phenyl-1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (6). Method 1. Oxidation of 5 Using $KMnO_4$. Tetrahydro compound **5** (0.24 g) was dissolved in acetone (50 ml) and $KMnO_4$ (1 g) was added to it. The mixture was refluxed on water bath for 8 h. The solution was filtered and acetone was distilled off from the filtrate. The residue thus obtained was taken in water (25 ml) and excess of $KMnO_4$ was destroyed with sodium sulfite solution (20 ml). The solution was extracted with chloroform (3×50 ml) and chloroform extract was dried over anhydrous sodium sulfate and the solvent was distilled off. The crude product thus obtained was recrystallized from pet. ether (60—80 °C)-benzene, mp 152 °C, yield 82%.

Found: C, 70.73; H, 4.60; N, 17.75%. Calcd for: C, 70.88; H, 4.64; N, 17.70%.

Method 2. Oxidation of 5 Using *N*-Benzylideneaniline (2a). Tetrahydro compound **5** (0.24 g) was dissolved in methanol (8 ml) and *N*-benzylideneaniline (**2a**, 0.18 g) was added to it. Reaction mixture was thoroughly shaken and left aside for few minutes. Separated light yellow-colored crystalline product (**6**) was filtered and recrystallized from pet. ether (60—80 °C)-benzene, mp 152 °C, yield 74%.

Method 3. From 2-Aminobenzohydrazide (1) and *N*-Benzylideneaniline (2a). 2-Aminobenzohydrazide (**1**, 0.15 g) was dissolved in minimum amount of methanol (6 ml) and *N*-benzylideneaniline (**2a**, 0.36 g) was added to it. Reaction mixture was thoroughly stirred and left aside for few minutes. Light yellow-colored crystalline compound separated out from the clear solution within few minutes. It was filtered and recrystallized from pet. ether (60—80 °C)-benzene, mp 152 °C, yield 72%.

***N*-(2-Methylaminobenzoyl)-*N'*-benzylidenehydrazines (8). General Procedure.** 2-(Methylamino)benzohydrazide (**7**, 1 mmol) was dissolved in methanol (7 ml) and an *N*-benzylideneaniline (**2**, 1 mmol) was added to it. The reaction mixture was stirred and left aside for few minutes. **8** separated immediately from the clear solution. It was filtered and recrystallized from suitable solvent (Table 1).

2-[2-(Methylamino)phenyl]-5-aryl-1,3,4-oxadiazoles (9). General Procedure. Method 1. Oxidation of Hydrazones 8 with $KMnO_4$. Hydrazone **8** (1 mmol) was dissolved in dry acetone (50 ml) and $KMnO_4$ (1 g) was added to it. The mixture was refluxed on water bath for 8 h. Further quantities of $KMnO_4$ were added to boiling solution until the pink color persisted. The solution was filtered and acetone was distilled off from the filtrate. The residue thus obtained was taken in water (20 ml) and excess of $KMnO_4$

was destroyed with sodium sulfite solution (20 ml). The solution was extracted with chloroform (3×50 ml) and chloroform extract was dried over anhydrous sodium sulfate and the solvent was distilled off. The crude product thus obtained was recrystallized from suitable solvent (Table 2).

Method 2. Oxidation of Hydrazones 8 with LTA. Hydrazone **8** (1 mmol) was dissolved in dry benzene (25 ml). Dry LTA (2 mmol, 0.886 mg) was added to it and the reaction mixture was refluxed on water bath for 15 min and then cooled. The mixture was extracted with 30% NaOH solution (3×50 ml). Benzene solution was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The obtained brown residue was purified by recrystallization from suitable solvent (Table 2).

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