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Note

Synthesis of 2-(2-aminophenyl)-3-hydroxyquinazolin-4(3*H*)-one — A synthon of quinazolino [3,2-*d*][3,1,4]benzoxadiazepinones

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Synthesis of 2-(2-aminophenyl)-3-hydroxyquinazolin-4(3*H*)-one by a novel ring contraction rearrangement is reported.

As part of our ongoing search for 2,3-annelated quinazolin-4(3*H*)-ones of biological importance, we planned to synthesise quinazolino [3,2-*d*][3,1,4] benzoxadiazepin-9-one ring system and the cyclic hydroxamic acid, 2-(2-aminophenyl)-3-hydroxyquinazolin-4(3*H*)-one **4a** was identified as a suitable precursor. We report herein two alternative syntheses of **4**, involving a novel Heindel type ring contraction rearrangement.[1]

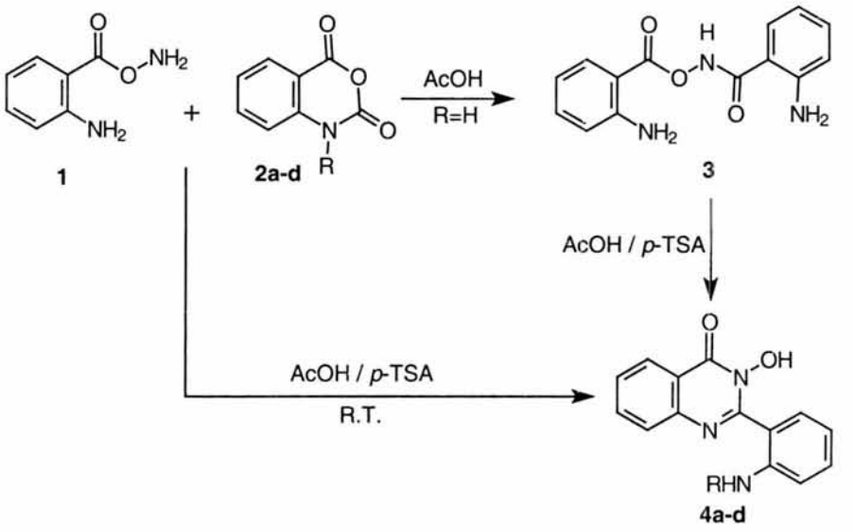
An acetic acid solution of *O*-(2-amino-benzoyl)-hydroxylamine (**1**, ABHA)[2] and isatoic anhydride **2a** containing catalytic amount of *p*-toluenesulphonic acid was stirred at room temperature for 12 hr. 2-(2-aminophenyl)-3-hydroxyquinazolin-4-(3H)-one (**4a**, M^+ at m/z 253) (**Table I**) separated out from the reaction mixture in 56% yield, and contains (vide infrared) NH_2 (3371, 3316 cm^{-1}), CO(1667 cm^{-1}) and N-OH (br, ~3033 cm^{-1}) functional groups.

The mass spectrum (EI-MS) exhibited an intense peak at m/z 237 (M^+ -16), and its alcoholic solution gave dark red colour with aqueous ferric chloride, both features reminiscent of cyclic hydroxamic acid.[3,4] When the reaction was conducted in acetic acid only, *O*-(2-aminobenzoyl)-*N*-(2-aminobenzoyl) hydroxylamine [**3**, IR (KBr): 3490 and 3460; 3390 and 3375 (NH_2), 3315 (NH), 1720, 1675 (CO)] was formed. Compound **3** could independently be converted to **4a** by stirring in acetic acid containing *p*-toluenesulphonic acid. The formation of **4a** from **3** is interesting and proceeds in all probability via the intermediate, 2-(2-aminophenyl)[4,1,3] benzoxadiazepin-5-one **5**, which undergoes Heindel type of ring contraction rearrangement (**Scheme I**).

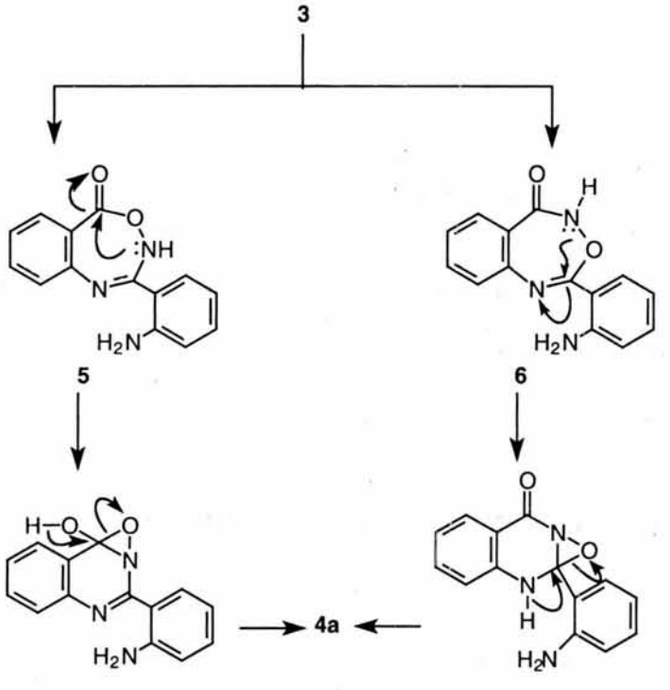
The intermittent formation of 2-(2-aminophenyl)[3,1,4]benzoxadiazepin-5-one **6** in the reaction was equally possible, but was ruled out since *N*-substituted anhydrides **2b-d** also yielded cyclic hydroxamic acids **4a-d** when reacted with **1** in acetic acid containing *p*-toluenesulphonic acid.

Table I — Physical and spectral data of 2(2-amino/alkylaminophenyl)-3-hydroxy-quinazolin-4(3*H*)-ones **4a-d**

Compd.	m p (°C)	Yield (%)	Mass ($M^{+\cdot}$)	UV (MeOH) λ_{max} (nm)	IR (KBr), cm^{-1}		^1H NMR (δ ppm)
					Amine	C=O	
4a	258	56	253	304	3371	1667	6.6-7.9 (m, 7H, Ar-H),
				270	3316		8.2 (d, 1H, per Ar-H).
				231			
4b	221	42	267	309	3418	1658	2.9 (s, CH_3), 6.8-7.8
				271			(m, 7H, Ar-H), 8.3
				235			(d, 1H, per Ar-H)
4c	177	48	--	305	3384	1660	1.25 (t, 3H, CH_3),
				269			3.15 (q, 2H, CH_2),
				259			6.7-7.9 (m, 7H, Ar-H),
							8.3 (d, 1H, peri Ar-H)
4d	171	49	--	309	3401	1670	4.4 (s, 1H, CH_2),
				273			6.7-7.8 (m, 12H, Ar-H),
				251			8.25 (d, 1H, peri Ar-H).

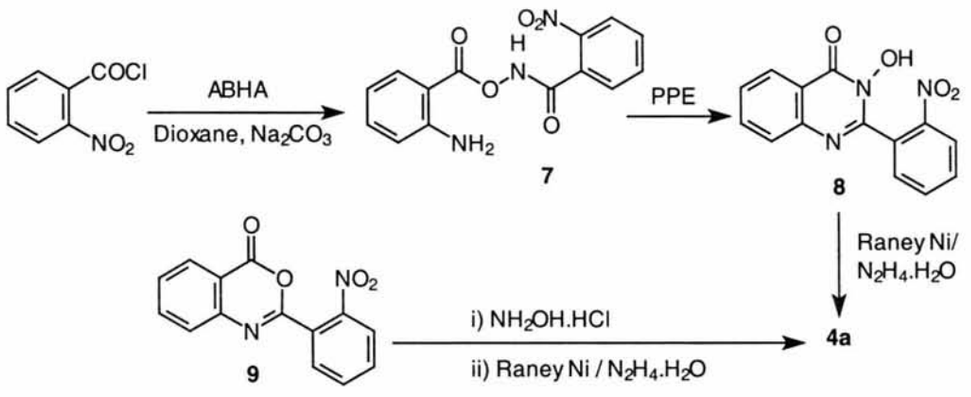


2/4	a	b	c	d
R	H	CH_3	C_2H_5	CH_2Ph

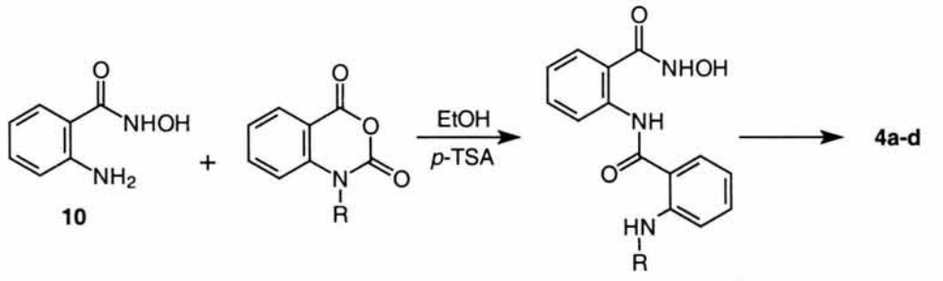


Scheme I

Further, **1** was benzoylated with 2-nitrobenzoyl chloride to isolate O-(2-aminobenzoyl)-*N*-(2-nitrobenzoyl)hydroxylamine **7**.[5] In polyphosphate ester, **7** directly gave 2-(2-nitrophenyl)-3-hydroxy-quinazolin-4(3*H*)-one **8** which responded to characteristic chemical test of cyclic hydroxamic acid. This result proves the transient formation of [4,1,3]benzo-xadiazepin-5-one but not [3,1,4] benzoxadiazepin-5-one, as **7** cannot yield the latter. Reduction of nitro group in **8** with hydrazine hydrate / Raney Ni at room temperature



Scheme II



Scheme III

yielded **4a** (**Scheme II**). The structure of **8** was confirmed by an independent synthesis from 2-(2-nitrophenyl)-3,1-benzoxazin-4-one **9**[6] following Legrand's method.[7]

The alternative method of synthesising **4** (in 90% yield) involves refluxing a mixture of 2-aminobenzhydroxamic acid **10**, an isomer of **1**, and isatoic anhydride **2a** in ethanol containing catalytic amount of *p*-toluenesulphonic acid (**Scheme III**) affording a simple and direct synthesis of the title synthon.

Experimental Section

Melting points were determined in capillaries using Polman digital melting point apparatus (MP 96) and reported in °C. UV spectra were recorded in methanol on Shimadzu 160 spectrophotometer, IR spectra in KBr pellets on Shimadzu 435, ^{1}H NMR spectra on Varian Gemini-200 MHz instrument and mass spectra on VG-micromass 70-70H instrument at 70 eV.

***O*-(2-Aminobenzoyl)-*N*-(2-aminobenzoyl)hydroxylamine 3.** To a solution of *O*-(2-aminobenzoyl)-hydroxylamine (**1**, 1.52 g) in acetic acid (12 mL) was added isatoic anhydride (**2a**, 1.63 g), and the mixture was stirred at room temperature for 8 hr. *O*-(2-Aminobenzoyl)-*N*-(2-aminobenzoyl) hydroxylamine **3** that separated out was filtered and recrystallised from ethanol, yield 1.8 g (69%), m.p. 232°C; IR: 3490, 3460, 3390, 3375, 3315, 1720, 1675, 1588, 1530, 1496, 1447, 1329, 1284, 1240, 1210, 905, 790.

2-(2-Amino/alkylaminophenyl)-3-hydroxy-quinazolin-4(3*H*)-one 4a-d.

General procedure: **Method-A**. A mixture of *O*-(2-aminobenzoyl) hydroxylamine (**1,** 1.52 g) isatoic anhydride (**2a**, 1.63 g) / *N*-alkyl isatoic anhydride **2b-d** and a pinch of *p*-toluenesulphonic acid in acetic acid (8 mL) was stirred at room temperature for 14-20 hr. A crystalline product (**4a-d**) that separated out in 42-56% yields was filtered, washed with water, and recrystallised from methanol.

Method-B. To a solution of 2-aminobenzhydroxamic acid (**10**, 1.52 g) and isatoic anhydride (**2a**, 1.63 g) / *N*-alkyl isatoic anhydride **2b-d** in ethanol (20 mL), a pinch of *p*-toluenesulphonic acid was added. The mixture was refluxed for 4 hr, 2-(2-amino/alkylaminophenyl)-3-hydroxyquinazolin-4(3*H*)-one **4a-d** separated out as colourless crystalline solid on cooling the reaction mixture. It was filtered and recrystallised from methanol, yield 71-90%. These

samples were identical (mp mmp, superimposable IR) with those obtained in Method-A.

2-(2-Nitrophenyl)-3-hydroxy-quinazolin-4(3H)-one 8. To a solution of 2-(2-nitrophenyl)-3,1-benzoxazin-4-one (**9**, 2.68 g) in ethanol (20 mL), an aq. solution of hydroxylamine hydrochloride (1.38 g in 5 mL of water) was added, and the mixture was refluxed for 2 hr. when clear solution was obtained. At this stage, 2 mL of 10% aq. NaOH was added dropwise to the reaction mixture, and the refluxing continued for 30 min. The excess solvent was removed in *vacuo*. The resulting 2-(2-nitrophenyl)-3-hydroxyquinazolin-4(3*H*)-one **8** was filtered and recrystallised from ethanol, yield 2.2 g (78%), m.p. 201-202°C; UV: 318 (log ε 3.82), 263 (log ε 3.67) and 220 (log ε 3.47). IR: 3120 (br), 1675, 1607, 1588, 1526, 1450, 1389, 1348.

2-(2-Aminophenyl)-3-hydroxy-quinazolin-4(3*H*)-one 4a. To a solution 2-(2-nitrophenyl)-3-hydroxyquinazolin-4(3*H*)-one (**8**, 1.15 g) in 10 mL of ethanol, activated Raney Ni (0.8 g) and hydrazine hydrate(99-100%, 0.5 mL) was added, and the reaction mixture was allowed to stand at room temperature for 30 min. and filtered to remove Raney Ni. The filtrate was concentrated and poured in ice cold water (50 mL) when 2-(2-aminophenyl)-3-hydroxyquinazolin-4(3*H*)-one **4a** separated out. It was filtered and recrystallised from methanol, yield 0.62 g (62%), m.p. 258°C.

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