Synthesis of Indolylquinazolinone: A Novel Bisazaheterocycle

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Received 10 December 1999; revised 1 March 2000

Abstract: A facile synthesis of 2-(2-aryl-1*H*-7-indolyl)-3,4-dihydroquinazolin-4-ones is reported.

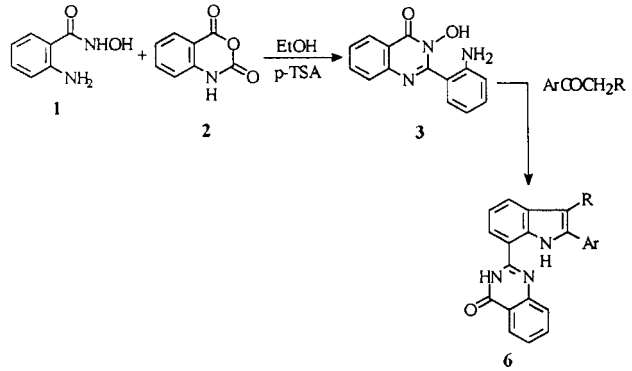
Key words: hydroxamic acids, indoles, ketones, amides, condensation, heterocycles

Our interest in developing quinazolinone based heterocycles prompted us to react 2-(2-aminophenyl)-3-hydroxyquinazolin-4(3*H*)-one (**3**) with aralkyl ketones. The aim was to isolate quinazolino[3,2-*d*][3,1,4]benzoxadiazepin-9-ones (**4**) by bridging with carbon the *N*-hydroxyl and amino groups in **3**. But surprisingly the reaction yielded 2-(2-aryl-1*H*-7-indolyl)-3,4-dihydroquinazolin-4-ones (**6**), providing a facile synthetic route for the less known indolyl quinazolinones which are anti-inflammatory, psychotrophic agents,[1,2] CCK receptors[3] and CNS active as well as depressant agents.[4]

The cyclic hydroxamic acid **3** was prepared in one-step from 2-aminobenzhydroxamic acid (**1**) and isatoic anhydride (**2**). Refluxing an equimolar mixture of **3** and 4-methylacetophenone in nitrobenzene for 6 hours, followed by usual workup yielded a crystalline solid (M^+ at *m*/*z* 351) (Scheme 1). It is devoid of N−OH group (negative $FeCl_3$ color test).[5] The UV spectrum showed two absorption maxima at λ_{max} = 327.7 nm and 266.7 nm, respectively and appeared as a combination spectrum of 2-phenylindole (328 nm) and quinazolin-4(3*H*)-one (265 nm) rings.[6,7] The presence of indole moiety was further evident from the signals at δ = 6.6 (s, l H, 3-H) and 7.95 (NH, D_2O exchangeable). On adding D_2O, the 3-H signal shifted to downfield (δ = 6.8), a characteristic feature of indoles.[8] The appearence of a doubly charged ion peak (at *m*/*z* 176) is also reminiscent of indoles.[9]

The quinazolinone moiety revealed itself by the appearence of CO peak (ν = 1702 cm^{-1}) in the IR spectrum and the peri-proton signal as doublet at δ = 8.2 in the ^1H NMR spectrum. The ^{13}C NMR spectrum revealed a total of 19 different carbons including quinazolinone carbonyl (δ = 156.9), azomethine carbon (δ = 153.3) and C_3 of indole (δ = 108.6).

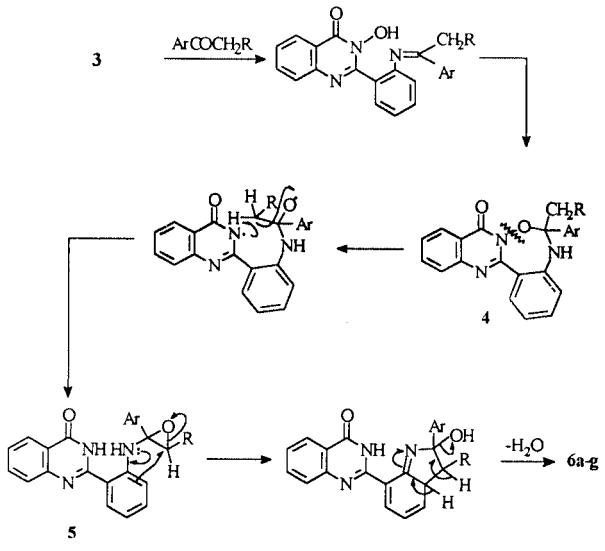
The reaction was extended to six other aralkyl ketones (Scheme 1), and in each case the corresponding 2-(2-aryll*H*-7-indoyl)-3,4-dihydroquinazolin-4-one was isolated and characterized. As expected, there is no peak around δ = 6.6 in the ^1H NMR spectra for the products obtained with propiophenone and dibenzyl ketone, to confirm that C_3 of indole carried substituents in **6f** and **6g** (see experimental scetion).



6	a	b	c	d	e	f	g
Ar	C_6H_5	4-$H_3CC_6H_4$	4-ClC_6H_4	4-$O_2NC_6H_4$	2-HOC_6H_4	C_6H_5	$CH_2C_6H_5$
R	H	H	H	H	H	CH_3	C_6H_5

Scheme 1

The mechanism of formation of **6** is both interesting and intriguing (Scheme 2). We presume that the reaction proceeds via a transient quinazolino[3,2-*d*][3,l,4]benzoxadiazepin-9-one **4** and 2-(2-oxirinylaminophenyl)quinozolin-4(3*H*)-one **5**. Intramolecular oxygenation of C=N in cyclic hydroxamic acids was reported earlier from our laboratories.[10]



Scheme 2

2-(2-Aminophenyl)-3-hydroxyquinazolin-4(3*H*)-one (3)
To a solution of 2-aminobenzhydroxamic acid (**1**; 1.52 g, 10 mmol) and isatoic anhydride (**2**; 1.63 g, 10 mmol) in EtOH (20 mL) was added a pinch of *p*-toluenesulfonic acid. The mixture was refluxed for 4 h. On cooling, the title compound separated out as colorless crystalline solid. It was filtered, and recrystallized from MeOH; yield: 2.28 g (90%); mp 258 °C.

UV (MeOH): λ_{max} (log ε) = 304 (3.91), 270 (3.84), 231 nm (3.41).

IR (KBr): ν = 3371, 3316, 3033 (br), 1667, 1609, 1589, 1574, 1415, 1317 cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): δ = 6.6−7.9 (m, 7 H, Ar-H), 8.2 (d, 1 H, *J* = 10 Hz, peri Ar-H).

MS: *m*/*z* = 253 (M^+ 100), 237, 236, 223, 120, 119, 118, 92, 91, 90, 77, 63.

2-(2-Aryl-1*H*-7-indolyl)-3,4-dihydroquinazolin-4-ones 6a−g; General Procedure
A mixture of **3** (0.8 g, 3 mmol) and the appropriate aralkyl ketone (3 mmol) was dissolved in nitrobenzene (10 mL, bp 210−211 °C) and refluxed for 6 h. On cooling the reaction mixture, the corresponding 2-(2-aryl-l*H*-7-indolyl)-3,4-dihydro-4-quinazolinone **6** separated out from the clear solution as a colorless crystalline solid. It was filtered, dried and passed over a column of neutral alumina (~150 mesh) using EtOAc as eluent (7 × 30 mL). The analytical (satisfactory microanlyses obtained: C ±0.39, H ±0.20, N ±0.11) and spectral data of compounds **6a−g** prepared are listed below. Compounds **6d** and **6e** were not sufficiently soluble in the usual NMR solvents and hence their ^{1}H NMR spectra were not recorded.

6a
Yield: 68%; mp 298 °C.

UV (MeOH): λ_{max} = 327.4, 266.7 nm.

IR (KBr): ν = 3126br (N−H), 1700 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6/TMS): δ = 6.65 (s, 1 H, 3-H_{indole}), 6.95−7.90 (m, 11 H, Ar-H), 8.1 (s, 1 H, indole NH), 8.25 (d, 1 H, *J* = 8 Hz, peri ArH), 11.2 (s, 1 H, amide NH).

MS: *m*/*z* = 337 (M^+).

6b
Yield: 81%; mp >320 °C.

UV (MeOH): λ_{max} = 327.7, 266.7 nm.

IR (KBr): ν = 3119br (N−H), 1702 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6/TMS): δ = 2.39 (s, 3 H, CH_3), 6.6 (s, 1 H, 3-H_{indole}), 6.95−8.10 (m, 10 H, Ar-H), 7.95 (s, 1 H, indole NH), 8.25 (d, 1 H, *J* = 10 Hz, peri Ar-H), 11.2 (s, 1 H, amide NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 156.9, 153.3, 149.2, 140.5, 139.8, 135.2, 130.9, 130.6, 129.7, 129.5, 128.9, 127.2, 127.0, 123.6, 122.1, 121.1, 118.2, 109.4, 108.6, 20.9.

MS: *m*/*z* = 351 (M^+).

6c
Yield: 78%; mp 318 °C.

UV (MeOH): λ_{max} = 325.9, 264.6 nm.

IR (KBr): ν = 3128br (N−H), 1702 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6/TMS): δ = 6.6 (s, 1 H, 3-H_{indole}), 6.95−7.9 (m, 10 H, Ar-H), 8.1 (s, 1 H, indole NH), 8.25 (d, 1 H, *J* = 10 Hz, peri Ar-H), 11.2 (s, 1 H, amide NH).

MS: *m*/*z* = 371 (M^+).

6d
Yield: 74%; mp 317 °C.

UV (MeOH): λ_{max} = 327.4, 266.1 nm.

IR (KBr): ν = 3062br (N−H), 1699 cm^{-1} (C=O).

MS: *m*/*z* = 382 (M^+).

6e
Yield: 71%; mp 296 °C.

UV (MeOH): λ_{max} = 329.1, 267.4 nm.

IR (KBr): ν = 3066br (N−H), 1710 cm^{-1} (C=O).

MS: *m*/*z* = 353 (M^+).

6f
Yield: 69%; mp 316 °C.

UV (MeOH): λ_{max} = 328.4, 266.9 nm.

IR (KBr): ν = 3066br (N−H), 1708 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6/TMS): δ = 2.00 (s, 3 H, CH_3), 7.20-7.65 (m, 12 H, Ar-H), 8.25 (d, J = 10 Hz, peri Ar-H), 11.2 (s, 1 H, amide NH). Indole NH signal was found to be merged with Ar-H.

MS: *m*/*z* = 351 (M^+).

6g
Yield: 79%; mp 312 °C.

UV (MeOH): λ_{max} = 328.1, 265.4 nm.

IR (KBr): ν = 3066br (N−H), 1709 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6/TMS): δ = 3.95 (s, 2 H, CH_2), 7.00−7.78 (m, 16 H, Ar-H), 7.9 (s, 1 H, indole NH), 8.2 (d, 1 H, *J* = 10 Hz, peri Ar-H), 11.5 (s, 1 H, amide NH).

MS: *m*/*z* = 427 (M^+).

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Article Identifier:
1437-210X,E;2000,0,09,1217,1218,ftx,en;Z09099SS.pdf