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Synthesis of 2-Substituted-2,3-dihydro-4(1*H*)quinazolinones using Sodium Bisulfate as a Catalyst by the Grinding Technique

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2,3-Dihydro-4(1*H*)-quinazolinones are a class of heterocycles that have drawn much attention due to their biological activities.^{1–3} However, the conventional methods for their synthesis require drastic conditions. For example, in 1960 Böhme and Böing reported 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones could be prepared by stirring 2-anthranilamide and aldehydes or ketones in the presence of conc. HCl in absolute ethanol.⁴ Recently, the synthesis of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones using Lewis acids and heteropoly acids such as SmI₂,⁵ Sc(OTf)₃,⁶ NH₄Cl,⁷ and H₃PW₁₂O₄₀⁸ as catalysts has been described and their catalyst-free synthesis in ionic liquids or 2,2,2-trifluoroethanol has also been reported.^{9,10} However, certain drawbacks such as costly reagents, harmful solvents, large excess of raw material and catalysts, and low yields are associated with some of these procedures. Moreover, all these reactions proceeded with mechanical stirring. We now describe a simple, novel and efficient protocol for the preparation of 2-substituted-2,3-dihydro-4(1*H*)-quinazolinones in the presence of NaHSO₄ and water by the grinding technique (*Scheme 1*).

In a mortar, an equimolar mixture of 2-anthranilamide and the aldehyde (or ketone), NaHSO₄ (2 mol %) and water (1 mL) were added. The mixture was ground well at room temperature for 10 min, and then heated at 60°C for the appropriate period of time (*Table 1*). Aromatic aldehydes carrying either electron-withdrawing (NO₂ and Cl) or electron-donating groups (CH₃, OCH₃, OH and N(CH₃)₂) were all suitable for use (**3a–3m**). The position of the substituents on the aromatic ring had no effect on this conversion. The cyclocondensation of 2-anthranilamide with ketones required comparatively longer reaction time than that with aromatic aldehydes (**3n** and **3o**). Aliphatic aldehydes failed to give the corresponding 2,3-dihydro-4(1*H*)-quinazolinones (**3p** and **3q**). The same

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reaction with ammonium chloride⁷ as acid catalyst gave lower or no yield at all in some cases.

The effect of water on the product yields was investigated using a model reaction between 2-anthranilamide and benzaldehyde. In the presence of 2 mL water, 92% yield was obtained but required 1 h longer. Furthermore, we observed that a much lower yield (78%) was produced under solvent-free conditions.

	R ₁		Usating	Yield (%) 94	mp (°C)	
Product		R_2	time (h)		Found 225–227	<i>lit.</i> 224–226 ¹¹
3a		Н	0.5			
3b	$2-NO_2C_6H_4-$	Н	1.0	95	191–193	191–194 ¹¹
3c ^a	$3-NO_2C_6H_4-$	Η	1.0	97	200-202	see Table 2
3d ^a	$4-NO_2C_6H_4-$	Η	1.0	90	198-200	see Table 2
3e	$2-ClC_6H_4-$	Η	1.5	92	202-204	see Table 2
3f	$4-ClC_6H_4-$	Η	1.5	96	204-206	$205 - 206^{10}$
3g	2,4-Cl ₂ C ₆ H ₃ -	Η	1.5	93	174–176	181-185 ¹²
3h	$4-CH_3C_6H_4-$	Н	2.0	71	224-225	$225 - 227^5$
3i	4-CH ₃ OC ₆ H ₄ -	Н	1.5	84	182–184	$180 - 182^5$
3j	$2-HOC_6H_4-$	Η	2.0	85	222-224	see Table 2
3k	$4-HOC_6H_4-$	Н	1.5	73	210-212	see Table 2
31	4-HO-3-CH ₃ OC ₆ H ₃ -	Η	1.0	75	219-221	see Table 2
3m ^{a, b}	4-(CH ₃) ₂ NC ₆ H ₄ -	Н	2.0	82	205-207	see Table 2
3n	-(CH ₂) ₅ -		3.0	83	224-226	$225 - 226^5$
30 ^c	C ₆ H ₅ -	CH ₃	7.0	54	222-224	$225 - 229^{11}$
3р	CH ₃ CH ₂ -	Н	8.0	0		_
3q	C ₆ H ₅ CH ₂ -	Н	8.0	0		

Table 1
Reaction of 2-Anthranilamide with Aldehydes and Ketones in the Presence of NaHSO4

a) Yellow solid. b) p-Dimethylaminobenzaldehyde (6.5 mmol) was used. c) Acetophenone (6.5 mmol) was used.

C mpd	mp (°C)	C	H	N	IR (cm^{-1})	¹ H NMR (δ)
<u>3</u> c	200–202	62.45 (62.56)	4.12 (4.08)	15.61 (15.50)	3337 3147 1673	8.76 (d, $J = 7.4$ Hz, 2H, ArH), 8.42 (t, J = 7.5 Hz, 2H, ArH), 7.97 (brs, 1H, NH-CO), 7.87 (dt, $J = 6$, 7.5 Hz, 2H, ArH), 7.62 (brs, 1H, NH), 7.57 (t, $J = 6.2$ Hz, 1H, ArH), 7.39 (t, $J = 7.5$ Hz, 1H, ArH), 7.26 (s, 1H, CH)
3d	198–200	62.45 (62.33)	4.12 (4.08)	15.61 (15.70)	3363 3291 1661	8.53 (s, 1H, NH-CO), 8.27 (d, $J =$ 8.6 Hz, 2H, ArH), 7.76 (d, $J =$ 8.6 Hz, 2H, ArH), 7.64 (d, $J =$ 7.6 Hz, 1H, ArH), 7.33 (s, 1H, NH), 7.29 (t, $J =$ 7.4 Hz, 1H, ArH), 6.79 (d, $J =$ 8.1 Hz, 1H, ArH), 6.71 (t, $J =$ 7.4 Hz, 1H, ArH) 5.93 (s, 1H, CH)
3e	202–204	65.00 (64.88)	4.29 (4.34)	10.83 (10.75)	3362 3196 1647	8.21 (s, 1H, NH-CO), 7.67 (d, $J =$ 7.8 Hz, 2H, ArH), 7.50–7.47 (m, 1H, ArH), 7.41–7.38 (m, 2H, ArH), 7.27 (t, J = 6.8 Hz, 1H, ArH), 7.01 (s, 1H, NH), 6.78 (d, $J =$ 7.8 Hz, 1H, ArH), 6.73 (dd, $J =$ 6.8, 7.9 Hz, 1H, ArH), 6.14 (s, 1H, CH)
3j	222–224	69.99 (70.10)	5.04 (4.98)	11.66 (11.57)	3410 3157 1647	9.85 (s, 1H, NH-CO), 7.93 (s, 1H, NH), 7.64 (d, $J = 7.0$ Hz, 1H, ArH), 7.36 (d, J = 7.5 Hz, 1H, ArH), 7.24 (t, $J =7.1 Hz, 1H, ArH), 7.16(t, J = 7.5 Hz, 1H, ArH), 6.88 (d, J =8.0 Hz, 1H, OH), 6.81–6.74 (m, 3H,ArH), 6.68 (t, J = 7.5 Hz, 1H, ArH),6.01 (s, 1H, CH)$
3k	210–212	69.99 (70.12)	5.04 (5.11)	11.66 (11.57)	3338 3184 1670	9.52 (s, 1H, NH-CO), 8.14 (s, 1H, NH), 7.64 (d, $J = 7.5$ Hz, 1H, ArH), 7.33 (d, J = 8.5 Hz, 2H, ArH), 7.26 (t, $J =7.5 Hz, 1H, ArH), 6.94(t, J = 8.5 Hz, 1H, OH), 6.79–6.67 (m,4H, ArH), 5.67 (s, 1H, CH)$
31	219–221	66.66 (66.53)	5.22 (5.17)	10.36 (10.45)	3389 3354 1650	9.06 (s, 1H, NH-CO), 8.09 (s, 1H, NH), 7.62 (d, $J = 6.5$ Hz, 1H, ArH), 7.25 (dd, $J = 7.2$, 8.0 Hz, 1H, ArH), 7.09 (s, 1H, ArH), 6.94 (s, 1H, OH), 6.89 (d, $J = 6.5$ Hz, 1H, ArH), 6.77 (t, $J =$ 8.1 Hz, 2H, ArH), 6.69 (t, $J = 7.4$ Hz, 1H, ArH), 5.65 (s, 1H, CH), 3.76 (s, 3H, OCH ₃)
3m	205–207	71.89 (72.01)	6.41 (6.47)	15.72 (15.65)	3295 3192 1655	8.07 (s, 1H, NH-CO), 7.62 (d, <i>J</i> = 7.5 Hz, 1H, ArH), 7.31 (d, <i>J</i> = 8.6 Hz, 2H, ArH), 7.24 (dd, <i>J</i> = 7.2, 8.0 Hz, 1H, ArH), 6.92 (s, 1H, NH), 6.75–6.65 (m, 4H, ArH), 5.64 (s, 1H, CH), 2.87 (s, 6H, N(CH ₃) ₂)

 Table 2

 Spectral Data of Compounds 3c-3e, 3j-3m

A method for the synthesis of 2-substituted-2,3-dihydro-4(1H)-quinazolinones from 2-anthranilamide and various aldehydes or ketones by aqueous grinding technique has been elaborated, and it possesses the advantages of inexpensive catalyst, mild reaction conditions and clean procedure.

Experimental Section

Mps were determined using an RY-1 micromelting point apparatus. Infrared spectra were recorded on a Scimitar 2000 series Fourier Transform instrument of VARIAN.¹H NMR spectra were obtained on a Bruker AV-500 spectrometer in DMSO- d_6 using TMS as an internal standard. Mass spectra were determined on an Agilent 1100 series LC/MSD VL ESI instrument. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin Elmer).

General Procedure

An equimolar mixture of 2-anthranilamide (1, 0.68 g, 5 mmol) and an aldehyde (or ketone) (5 mmol), NaHSO₄ (0.012 g, 0.1 mmol) and water (1 mL) in a mortar were ground well with a pestle at room temperature for 10 minutes. Then the mixture in the mortar was placed in an oven and kept at 60° C for the appropriate time until the completion of reaction (checked by TLC using CHCl₃:MeOH, 95: 5). The reaction mixture was cooled to room temperature and the precipitated solid was collected and washed thoroughly with water. The products were purified further by crystallization from ethanol. The pure products were identified by mp, IR, ¹H NMR, MS, and elemental analysis. The procedure was carried out on 100 mmol scale of anthranilamide with essentially no change in the yield.

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