Synthesis of new *N*₃-substituted quinazolin-4(3*H*)one derivatives

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Abstract : Quinazolin-4-one (1) was synthesized by reacting anthranilic acid with excess of formamide, which was *N*-alkylated with chloroacetone to form quinazolin-4-one-3-yl propan-2-one (2). The interaction of 2 with phenylhydrazine, 2,4-dinitrophenylhydrazine and semicarbazide gave the corresponding hydrazones (3). Further, the treatment of 2 with hydrazine hydrate yielded hydrazino derivative (4) which was condensed with variously substituted aryl aldehydes to form the corresponding hydrazones (5). The compound 4 on cyclization with ammonium acetate gave tricyclic compound (6). Further, compound 2 on reaction with hydroxylamine hydrochloride yielded oxime (7), and the corresponding oxime carbamates (8) with phenyl isothiocyanate and phenyl isocyanate.

Keywords : Quinazolin-4-one, hydrazones, carbamates.

In view of biological activity of quinazolines¹, we report here the synthesis of some new *N*₃-substituted quinazolin-4(3*H*)ones. The condensation of quinazolin-4(3*H*)one (1) with chloroacetone in presence of anhydrous potassium carbonate gave *N*-alkylated-(quinazolin-4-one-3-yl)propan-2-one (2). The formation of 2 was explained by the appearance of two singlets encountered at δ 2.3 and 4.7 due to the COCH₃ and -N-CH₂-CO in its PMR spectrum and the appearance of IR band at 1722 and 1673 cm⁻¹ due to acyclic C=O and cyclic amido C=O respectively. The compound 2 on reacting with phenylhydrazine/2,4-dinitrophenylhydrazine/semicarbazide in presence of sodium acetate in methanol gave corresponding hydrazones (3). The disappearance of IR band at 1673 cm⁻¹ due to acyclic C=O and appearance of additional band at 1610 cm⁻¹ due to >C=N and its correct PMR spectrum supported their formation.

Compound 2 on reacting with hydrazine hydrate in presence of dry sodium acetate in methanol yielded hydrazino derivative (4). The appearance of IR band at 3467–3227 and 1610 cm⁻¹ due to NH₂ and C=N and disappearance of IR band at 1722 cm⁻¹ due to acyclic C=O supports its formation. Further, compound 4 on condensation with variously substituted aryl aldehydes in methanol under acidic condition gave the corresponding hydrazones (5). The appearance of =CH protons at δ 8.2 for arylidene derivatives in PMR spectrum and the disappearance of IR band at 3467–3227 cm⁻¹ due to NH₂ indicated their formation. The compound 4 on cyclization with ammonium acetate in acetic acid gave tricyclic quinazoline derivatives (6).

Scheme 1

The disappearance of IR band at 1673 cm⁻¹ due to cyclic amido C=O and another at 3467–3227 cm⁻¹ due to -NH₂ indicated its formation. Further, compound 4 was transformed into corresponding carbamates and thiocarbamates (9) by treating with phenylisocyanate and phenylisothiocyanate respectively. The formation of compounds 9 was established by their correct IR and NMR data.

Table 1. Physical and analytical data of hydrazones 3, 5 and carbamates 8, 9

Compd.	R	M.p. (°C)	Yield (%)	Molecular formula	Found/(Calcd.)		
					C	H	N
3b	2,4-(NO ₂) ₂ -C ₆ H ₅	195	71	C ₁₇ H ₁₄ O ₅ N ₆	53.5 (53.4)	7.0 (7.1)	21.8 (21.9)
3c	NH ₂ -CO-	237	78	C ₁₂ H ₁₃ O ₂ N ₅	60.6 (60.7)	5.1 (5.0)	27.1 (27.0)
5b	<i>o</i> -ClC ₆ H ₄ -	143	68	C ₁₈ H ₁₄ ON ₄	64.1 (64.0)	4.0 (4.1)	16.4 (16.5)
5c	<i>p</i> -ClC ₆ H ₄ -	214	68	C ₁₈ H ₁₄ ON ₄	64.1 (64.0)	4.0 (4.1)	16.4 (16.5)
5d	<i>o</i> -OHC ₆ H ₄ -	214	76	C ₁₈ H ₁₅ O ₂ N ₄	67.7 (67.7)	4.6 (4.7)	17.6 (17.5)
5e	<i>p</i> -OHC ₆ H ₄ -	185	72	C ₁₈ H ₁₅ O ₂ N ₄	67.6 (67.7)	4.8 (4.7)	17.4 (17.5)
5f	3,4,5-(OCH ₃) ₃ C ₆ H ₂ -	222	84	C ₂₁ H ₂₁ O ₄ N ₄	64.2 (64.1)	5.2 (5.3)	14.3 (14.2)
5g	C ₆ H ₅ CH=CH-	226	61	C ₂₀ H ₁₇ ON ₄	72.8 (72.9)	5.2 (5.1)	17.1 (17.0)
5h	<i>p</i> -OH, <i>m</i> -OCH ₃ C ₆ H ₃ -	220	76	C ₁₉ H ₁₇ O ₃ N ₄	65.4 (65.3)	4.7 (4.8)	16.1 (16.0)
5i	<i>o</i> -NO ₂ C ₆ H ₄ -	219	79	C ₁₈ H ₁₄ O ₃ N ₄	61.9 (61.8)	4.0 (4.1)	16.8 (16.7)
5j	<i>p</i> -N, N(CH ₃) ₂ C ₆ H ₄ -	256	74	C ₂₀ H ₂₀ ON ₅	69.4 (69.3)	5.6 (5.7)	20.1 (20.0)
5k	<i>o</i> -OH, <i>m</i> -OCH ₃ C ₆ H ₃ -	180	64	C ₁₉ H ₁₇ O ₃ N ₄	65.2 (65.3)	4.9 (4.8)	16.1 (16.0)
5l	<i>o</i> -CH ₃ C ₆ H ₄ CH=CH-	210	61	C ₂₁ H ₁₉ ON ₄	73.3 (73.4)	5.4 (5.5)	16.2 (16.3)
5m	<i>o</i> -SHC ₆ H ₄ -	228	59	C ₁₈ H ₁₅ ON ₄ S	64.5 (64.4)	4.3 (4.4)	16.8 (16.7)
5n	β -OH naphthyl	270	71	C ₂₂ H ₁₈ O ₂ N ₄	71.2 (71.3)	4.9 (4.8)	15.2 (15.1)
8b	-	242	82	C ₁₈ H ₁₆ O ₂ N ₄ S	61.4 (61.3)	4.6 (4.5)	15.8 (15.9)
9b	-	182	78	C ₁₈ H ₁₇ O ₂ N ₅	64.5 (64.4)	5.0 (5.1)	20.9 (20.8)

Further, compound 2 on interaction with hydroxylamine hydrochloride in 5% methanolic NaOH furnished an oxime (7). The formation of oxime 7 has been established by the appearance of a broad band around 3318–2862 cm⁻¹ in IR spectrum due to -OH. The compound 7 was transformed into their corresponding oxime carbamates by reacting them with phenylisocyanate and phenylisothiocyanate in THF. The disappearances of IR band around 3318–2862 cm⁻¹ due to -OH confirmed their formation (Scheme 1).

Experimental

All chemicals used were of A.R. grade and are used without further purification. Melting points were determined by open capillary method, and are uncorrected. All ¹H NMR spectra were scanned on a Bruker A-300 F-NMR spectrometer. IR spectra were recorded on a Perkin-Elmer 783 spectrophotometer. Purity of the products in addition to the elemental analyses was checked by TLC.

The quinazolin-4(1*H*)one (1) was prepared by reported method¹⁴.

1-(Quinazolin-4-one-3-yl)propan-2-one (2) :

The compound 1 (6 g, 0.04 mol) and chloroacetone (4.9 g, 0.04 mol) in dry acetone (25 ml), to which anhydrous potassium carbonate was added and the reaction mixture refluxed further for 12 h, cooled and the separated solid extracted with ether. After removal of ether under reduced pressure gave solid which was recrystallized from ethanol to furnish (2), m.p. 170 °C, yield 83% (Found : C, 65.4; H, 4.8; N, 13.7. C₁₁H₁₀O₂N₂ requires : C, 65.3; H, 4.9; N, 13.8%); IR (KBr) 1722 (C=O), 1673 cm⁻¹ (cyclic amido C=O); ¹H NMR (CDCl₃) 2.3 (3H, s, COCH₃), 4.7 (2H, s, N-CH₂), 7.2–8.1 (5H, m, Ar-H).

1-(Quinazolin-4-one-3-yl)-2-phenylhydrazonyl propane (3a) :

The mixture of compound **2** (0.2 g, 0.001 mol), phenylhydrazine hydrochloride (0.1 g, 0.001 mol) and sodium acetate (0.15 g) in 50% methanol was stirred for 1 h and the separated solid was filtered, washed with water and recrystallized from ethanol to get **3a**, m.p. 188 °C, yield 86% (Found : C, 69.7; H, 5.6; N, 19.2. $C_{17}H_{16}ON_4$ requires : C, 69.8; H, 5.5; N, 19.1%); IR (KBr) 1670 (cyclic amido C=O), 1610 cm^{-1} (C=N); 1H NMR (DMSO- d_6) 2.15 (3H, s, -CH₃), 4.8 (2H, s, CH₂), 7.2–8.2 (5H, m, Ar-H).

The mixture of compound **2** (2.2 g, 0.01 mol), hydrazine hydrate (1.2 g, 0.01 mol) and 5% methanolic NaOH (10 ml) was stirred for 1/2 h and separated solid was filtered and recrystallized from ethanol to furnish the compound **4**, m.p. 115 °C, yield 86% (Found : C, 61.2; H, 5.5; N, 25.8. $C_{11}H_{12}ON_4$ requires : C, 61.1; H, 5.3; N, 25.7%); IR (KBr) 3467–3277 (NH₂), 1673 (cyclic amido C=O), 1613 cm^{-1} (C=N); 1H NMR (CDCl₃) 2.18 (3H, s, CH₃), 4.7 (2H, s, CH₂), 7.2–8.1 (5H, m, Ar-H and N=CH).

1-(Quinazolin-4-one-3-yl)-2-(arylidenehydrazino) propane (5a) :

To the mixture of equimolar quantities of **4** (0.195 g, 0.0009 mol), *p*-methoxybenzaldehyde (0.122 g, 0.0009 mol) in methanol (10 ml) and 2–3 drops of acetic acid were added and the reaction mixture was heated on water bath for 15 min and the yellow solid obtained was filtered and recrystallized from ethanol, m.p. 196 °C, yield 84% (Found : C, 64.2; H, 5.4; N, 14.3. $C_{21}H_{21}O_4N_4$ requires : C, 64.1; H, 5.3; N, 14.2%); IR (KBr) 1675 (cyclic amido C=O), 1610 cm^{-1} (C=N); 1H NMR (DMSO- d_6) 2.25 (3H, s, =C-CH₃), 3.8 (3H, s, OCH₃), 4.6 (2H, s, N-CH₂), 7.15–8.2 (8H, m, Ar-H and N=CH).

3-Methyl-1,2,4-triazino(3,4-c)-quinazoline (6) :

The mixture of compound **4** (0.195 g, 0.0009 mol) and ammonium acetate (0.1 g, 0.0009 mol) in glacial acetic acid (10 ml) was heated on an oil bath till yellow colour of reaction mixture changed to dark brown. The reaction mixture then poured in ice-water mixture and neutralized with ammonia and kept overnight. The separated solid was filtered and recrystallized from ethanol, m.p. 171 °C, yield 76% (Found : C, 66.6; H, 5.1; N, 28.2. $C_{11}H_{10}N_4$ requires : C, 66.7; H, 5.0; N, 28.3%); IR (KBr) 1615 (C=N), 1600 cm^{-1} (C=C); 1H NMR (CDCl₃) 2.20 (3H, s, =C-CH₃), 4.85 (2H, s, N-CH₂), 7.2–8.15 (5H, m, Ar-H and N=CH).

1-(Quinazolin-4-one-3-yl)-2-oximino propane (7) :

To the solution compound **2** (0.5 g, 0.002 mol) in 5% methanolic NaOH (10 ml), hydroxylamine hydrochloride (0.03 g, 0.002 mol) was added and the reaction mixture stirred for 1 h. The product obtained was filtered, washed

with water and recrystallized from ethanol, m.p. 200 °C, yields 82% (Found : C, 60.7; H, 5.1; N, 19.4. $C_{11}H_{11}O_2N_3$ requires : C, 60.8; H, 5.0; N, 19.3%); IR (KBr) 3181–2862 (-OH), 1669 (cyclic amido C=O), 1625 cm^{-1} (C=N); 1H NMR (DMSO- d_6) 2.20 (3H, s, =C-CH₃), 4.7 (2H, s, N-CH₂), 7.2–8.15 (5H, m, Ar-H and N=CH), 11.2 (1H, s, D₂O exchangeable oxime -OH).

1-(Quinazolin-4-one-3-yl)-2-(O-aryl carbamyl)propane (8a) :

The mixture of compound **7** (0.1 g, 0.0005 mol) and phenyl isocyanate (0.05 g, 0.0005 mol) in THF was refluxed on a steam bath for 3 h and the separated solid was filtered and recrystallized from ethanol, m.p. 236 °C, yield 72% (Found : C, 64.2; H, 4.7; N, 12.5. $C_{18}H_{16}O_3N_4$ requires : C, 64.1; H, 4.8; N, 12.4%); IR (KBr) 3250 (NH), 1720 (cyclic amido C=O), 1628 cm^{-1} (C=N); 1H NMR (DMSO- d_6) 2.25 (3H, s, =C-CH₃), 4.6 (2H, s, N-CH₂), 7.15–8.5 (10 H, m, Ar-H and N=CH), 9.2 (1H, s, exchangeable with D₂O, NH).

1-(Quinazolin-4-one-3-yl)-2-(N-aryl carbamyl)propane (9a) :

The mixture of compound **4** (0.195 g, 0.0009 mol) and phenylisothiocyanate (0.176 g, 0.0009 mol) in THF was refluxed on a steam bath for 2 h and the separated solid was filtered and recrystallized from DMF, m.p. 164 °C, yield 64% (Found : C, 61.6; H, 4.7; N, 28.4. $C_{18}H_{17}ON_5S$ requires : C, 61.5; H, 4.8; N, 28.5%); IR (KBr) 3260 (NH), 1675 (cyclic amido C=O), 1615 cm^{-1} (C=N); 1H NMR (DMSO- d_6) 2.15 (3H, s, CH₃), 4.7 (2H, s, CH₂), 6.5 (1H, s, NH), 6.8 (1H, s, NH), 7.25–8.15 (10H, m, Ar-H and N=CH).

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