Cynogen Bromide and Ethylacetoacetate in Heterocyclization: Novel Synthesis of Tetracyclic Derivative of 3-Aryl Quinazolinones

M. B. Deshmukh,[a] Suresh S. Patil,[b]* Sanjeevani S. Patil,[b] and Swati D. Jadhav[b]

[a]Department of Organic Chemistry/AGPM, Shivaji University, Kolhapur, Maharashtra, India
[b]Department of Chemistry, PDVP Mahavidyalaya, Tasgaon, Maharashtra 416312, India
*E-mail: sanyujapatil@yahoo.com

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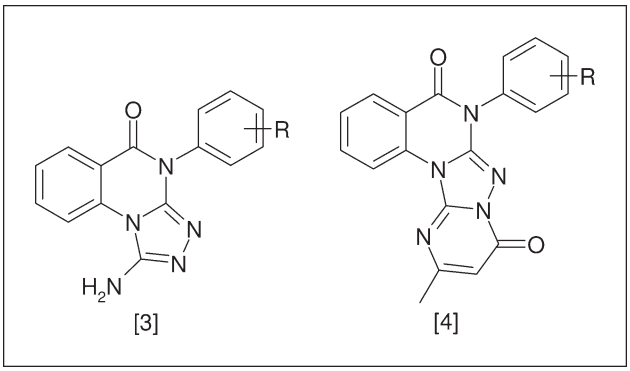

In this work, tricyclic 1-amino-4-(substituted phenyl)[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one **3** was synthesized by treatment of 2-hydrazinyl-3-(substituted phenyl)quinazolin-4(3*H*)-one **2** with cyanogen bromide, which on cyclization with ethylacetoacetate to get the targeted fused tetracyclic derivatives of quinazoli-4(3H)one **4**. The synthesized compounds have been characterized using IR and ^{1}H NMR, mass spectral data together with elemental analysis.

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INTRODUCTION

Quinazoline derivatives have attracted considerable attention due to their significant biological activities [1,2], especially antifungal [3,4], insecticidal [5], antihistaminic [6], anti-inflammatory [7], antibacterial [8], anticonvulsant [9,10], antithrombotic [11], antitubercular [12], and antitumor [13]. In this article, we report a new route for the synthesis of triazolo and tetracyclic derivatives of quinazolinone.

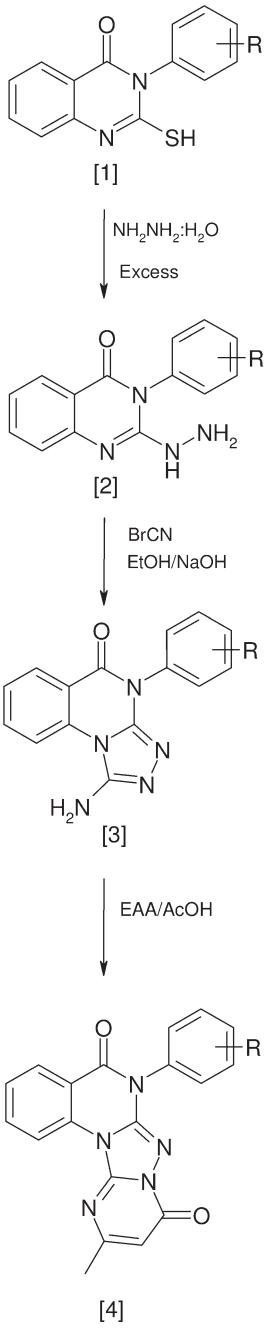
RESULT AND DISCUSSION

The new triazolo and tetracyclic derivatives of quinazolinone were prepared following the reaction sequences depicted in Scheme 1 and supported mechanism in Scheme 2. The starting compound **1** was prepared by sequential treatment of anthranilic acid with thiocarbamate salts of substituted aniline and carbon disulphide according to the reported method [14]. The appearance of broad band at 3330–3110 cm^{-1} in IR spectrum and a singlet displayed at δ, 10–11 ppm in the PMR spectrum due to —SH supports their formation. Compounds **1a–g** were heated with excess hydrazine hydrate to form 2-hydrazino derivatives **2a–g** in good yield [15]; the formation of which has been explained by the appearance of IR band at 3390–3300 cm^{-1} due to —NHNH$_2$ and disappearance of singlet displayed at δ, 10–11 ppm due to —SH and two additional singlets appeared between δ, 9–11 and δ, 2–6 ppm due to —NH and —NH$_2$ protons, respectively, in their PMR spectra. The condensation of **2** with cyanogens bromide in absolute alcohol gave the corresponding desired tricyclic amino triazoles **3a–g**; the formation of which was confirmed by the observation of a broad IR band at 3420–3000 cm^{-1} and singlet between δ, 3–6 ppm due to —NH$_2$ protons in their PMR spectrum. The compounds **3a–g** were cyclocondensed with ethylacetoacetate to get the targeted tetracyclic compounds **4a–g**. The formation of **4** has been established by the disappearance of singlet between δ, 3–6 due to —NH$_2$ protons and appearance of additional singlets due to Ar—CH$_3$ and =CH in their PMR spectrum.

EXPERIMENTAL

All melting points reported are incorrect and were determined by open capillary method. All chemicals used were of A.R. grade and have been used without further purification. IR spectra (in KBr, cm^{-1}) were recorded on a Perkin-Elmer 783 (FTIR) spectrophotometer. ^{1}H NMR spectra recorded in

Scheme 1



$CDCl_3$/DMSO-d_6 were scanned on a Bruker A-300 F-NMR spectrometer (Table 1). TMS was used as an internal standard with chemical shifts δ in ppm from down field to up field. Mass spectra were analyzed by EI technique on Shimadzu QP 2010 PLUS GC-MS system. The purity of products, in addition to the elemental analysis (Table 2), was checked by TLC.

3-(4-Methoxyphenyl)-2-sulfanylquinazolin-4(3*H*)-one (1). These compounds were prepared according to the reported method [14].

2-Hydrazinyl-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one (2a). A compound **la** (4.824 gm, 0.018 mol) was refluxed with 5 mL hydrazine hydrate in ethanol (15 mL) with constant stirring at 100°C for about 1.5 h, then cooled and thus the solid obtained was recrystallized from ethanol to furnish 2a [15], yield, 4.118 gm (86%), m.p. 207°C, IR: 3386–3328, 1664 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm), 2.65 (s, 3H, Ar—CH_3), 6.25(s, 2H, —NH_2), 6.9–8.1 (m, 8H, Ar—H), 10.9 (s, 1H, br, —NH); ms: m/z 282(12), 266(26), 251(45), 175(100), 107(55), 31(10). *Anal. Calcd.* for $C_{15}H_{14}O_2N_4$ (266): C, 63.82%; H, 5.00%; N, 19.85%. Found: C, 63.89%; H, 5.04%; N, 19.81%.

1-Amino-4-(4-methoxyphenyl)[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one (3a). A compound **2a** (5.054 gm, 0.019 mole) in ethanolic NaOH (50 mL) and cyanogen bromide (1 cm^3, 0.019 mole) were stirred for 3 h at room temperature. After neutralization of it with 10% sodium bicarbonate, the solid obtained was filtered and further recrystallized from ethanol to give **3a**, yield, 4.423 gm (80%), m.p. 270°C. IR: 3420–3010, 1685, 1615 cm^{-1}. ^1H NMR (DMSO-d_6): δ (ppm), 2.56 (s, 3H, Ar—CH_3), 5.62 (s, 2H, —NH_2), 7.1–8.2 (m, 8H, Ar—H); ms: m/z 307(50), 291(20), 276(62), 200(100), 107(72), 31(16). *Anal. Calcd.* for $C_{16}H_{13}ON_5$ (291): C, 62.53%; H, 4.26%; N, 22.79%. Found: C, 62.61%; H, 4.32%; N, 22.71%.

Scheme 2

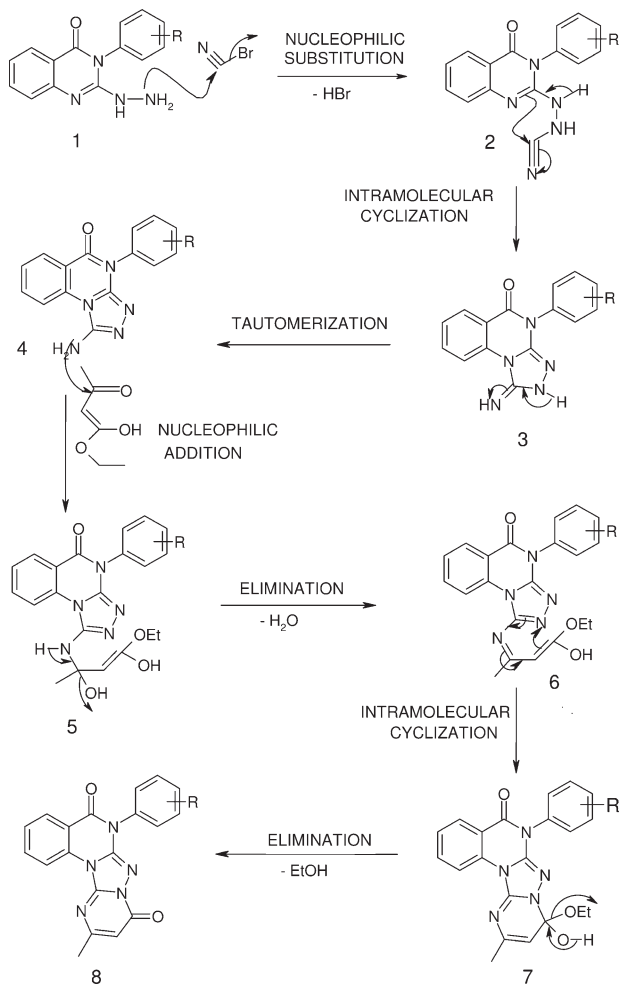


Table 1

Spectral characterization data of compounds **2**, **3**, and **4**.

Compound	IR(ν,cm^{-1}) KBr	H^1 NMR ($CDCl_3$/DMSO-d_6) δ(ppm)
2a	3386–3328 (—$HNNH_2$), 1660 (cyclic amido C=O), 1620 (C=N)	2.65 (s, 3H, Ar—OCH_3), 5.96(s, 2H, —NH_2), 6.9–8.1 (m, 8H, Ar—H), 10.9 (s(br), 1H, —NH)
2b	3372–3320 (—$HNNH_2$), 1654 (cyclic amido C=O), 1621 (C=N)	2.58 (s, 3H, Ar—CH_3), 2.95(s, 2H, —NH_2), 7.0–8.2 (m, 8H, Ar—H), 10.15 (s(br),1H, —NH)
2c	3381–3319 (—$HNNH_2$), 1670 (cyclic amido C=O), 1625 (C=N)	2.62 (s, 3H, Ar—CH_3), 3.74 (s, 2H, —NH_2), 6.9–8.1 (m, 8H, Ar—H), 11.00 (s(br),1H, —NH)
2d	3380–3332 (—$HNNH_2$), 1671 (cyclic amido C=O), 1622 (C=N)	2.61 (s, 3H, Ar—CH_3), 5.05 (s, 2H, —NH_2), 7.2–8.4 (m, 8H, Ar—H), 11.02 (s(br),1H, —NH)
2e	3390–3331 (—$HNNH_2$), 1664 (cyclic amido C=O), 1615 (C=N)	6.00 (s, 2H, —NH_2), 6.8–8.0 (m, 8H, Ar—H), 9.85 (s(br),1H, —NH)
2f	3376–3315 (—$HNNH_2$), 1669 (cyclic amido C=O), 1630 (C=N)	5.14(s, 2H, —NH_2), 7.0–8.3 (m, 8H, Ar—H), 9.51 (s(br),1H, —NH)
2g	3388–3330 (—$HNNH_2$), 1658 (cyclic amido C=O), 1628 (C=N)	2.86 (s, 2H, —NH_2), 6.9–8.0 (m, 8H, Ar—H), 10.79 (s(br),1H, —NH)
3a	3400–3100 (—NH_2), 1685 (cyclic amido C=O), 1615 (C=N)	2.56 (s, 3H, Ar—OCH_3), 5.62 (s, 2H, —NH_2), 7.1–8.2 (m, 8H, Ar—H)
3b	3410–3050 (—NH_2), 1690 (cyclic amido C=O), 1619 (C=N)	2.51 (s, 3H, Ar—CH_3), 3.72 (s, 2H, —NH_2), 7.0–8.1 (m, 8H, Ar—H)
3c	3390–3000 (—NH_2), 1684 (cyclic amido C=O), 1622 (C=N)	2.50 (s, 3H, Ar—CH_3), 3.91 (s, 2H, —NH_2), 7.2–8.2 (m, 8H, Ar—H)
3d	3416–3010 (—NH_2), 1681 (cyclic amido C=O), 1615 (C=N)	2.55 (s, 3H, Ar—CH_3), 4.22 (s, 2H, —NH_2), 7.1–8.0 (m, 8H, Ar—H)
3e	3395–3012 (—NH_2), 1689 (cyclic amido C=O), 1630 (C=N)	4.80 (s, 2H, —NH_2), 6.8–8.0 (m, 8H, Ar—H)
3f	3415–3090 (—NH_2), 1685 (cyclic amido C=O), 1625 (C=N)	6.00 (s, 2H, —NH_2), 7.1–8.3 (m, 8H, Ar—H)
3g	3400–3105 (—NH_2), 1687 (cyclic amido C=O), 1617 (C=N)	5.35 (s, 2H, —NH_2), 7.0–8.3 (m, 8H, Ar—H)
4a	1725–1690 broad and 1662 (cyclic amido C=O), 1626 (C=N)	2.44 (3H, s, Ar—OCH_3), 2.49 (s, 3H, =C—CH_3), 6.21 (1H, s, =CH), 7.2–8.4 (8H, m, Ar—H)
4b	1720–1691 broad and 1668 (cyclic amido C=O), 1618 (C=N)	2.51 (s, 3H, Ar—CH_3), 2.49 (s, 3H, =C—CH_3), 6.32 (s, 1H, =CH), 7.0—8.2 (m, 8H, Ar—H)
4c	1722–1693 broad and 1665 (cyclic amido C=O), 1615 (C=N)	2.38 (s, 3H, Ar—CH_3), 2.58 (s, 3H, =C—CH_3), 6.65 (s, 1H, =CH), 7.1–8.3 (m, 8H, Ar—H)
4d	1709–1696 broad and 1670 (cyclic amido C=O), 1620 (C=N)	2.40 (s, 3H, Ar—CH_3), 2.39 (s, 3H, =C—CH_3), 6.43 (s, 1H, =CH), 7.0–8.5 (m, 8H, Ar—H)
4e	1720–1684 broad and 1667 (cyclic amido C=O), 1622 (C=N)	2.45 (s, 3H, =C—CH_3), 6.22 (s, 1H, =CH), 7.2–8.2 (m, 8H, Ar—H)
4f	1730–1700 broad and 1675 (cyclic amido C=O), 1632 (C=N)	2.61 (s, 3H, =C—CH_3), 6.51 (s, 1H, =CH), 7.1–8.3 (m, 8H, Ar—H)
4g	1728–1697 broad and 1668 (cyclic amido C=O), 1625 (C=N)	2.51 (s, 3H, =C—CH_3), 6.40 (1H, =CH), 7.0–8.1 (m, 8H, Ar—H)

Table 2

Characterization data of compounds **2**, **3**, and **4**.

Compound	R groups	m.p. (°C)	Yield (%)	Molecular formula	Calcd (%) (Found)		
					C	H	N
2b	*o*-CH_3	209	86	$C_{15}H_{14}ON_4$	67.65 (67.59)	5.30 (5.38)	21.04 (21.10)
2c	*m*-CH_3	211	86	$C_{15}H_{14}ON_4$	67.65 (67.58)	5.30 (5.25)	21.04 (21.12)
2d	*p*-CH_3	205	76	$C_{15}H_{14}ON_4$	67.65 (67.72)	5.30 (5.35)	21.04 (21.09)
2e	*p*-Cl	218	82	$C_{14}H_{11}ON_4Cl$	58.65 (58.58)	3.87 (4.95)	19.54 (19.47)
2f	*m*-Cl	222	82	$C_{14}H_{11}ON_4Cl$	58.65 (58.55)	3.87 (4.80)	19.54 (19.60)
2g	*p*-Br	196	83	$C_{14}H_{11}ON_4Br$	50.78 (50.62)	3.35 (3.40)	16.92 (16.86)
3b	*o*-CH_3	269	78	$C_{16}H_{13}ON_5$	65.97 (65.91)	4.50 (4.58)	24.04 (24.16)
3c	*m*-CH_3	272	68	$C_{16}H_{13}ON_5$	65.97 (66.06)	4.50 (4.44)	24.04 (24.12)
3d	*p*-CH_3	265	72	$C_{16}H_{13}ON_5$	65.97 (65.98)	4.50 (4.49)	24.04 (23.99)
3e	*p*-Cl	278	70	$C_{15}H_{10}ON_5Cl$	57.80 (57.73)	3.23 (3.12)	22.47 (22.38)
3f	*m*-Cl	281	69	$C_{15}H_{10}ON_5Cl$	57.80 (57.71)	3.23 (3.11)	22.47 (22.51)
3g	*p*-Br	276	73	$C_{15}H_{10}ON_5Br$	50.58 (50.65)	2.83 (2.91)	19.66 (19.51)
4b	*o*-CH_3	308	70	$C_{20}H_{15}O_2N_5$	67.22 (67.16)	4.23 (4.11)	19.60 (19.52)
4c	*m*-CH_3	307	68	$C_{20}H_{15}O_2N_5$	67.22 (67.11)	4.23 (4.18)	19.60 (19.69)
4d	*p*-CH_3	302	69	$C_{20}H_{15}O_2N_5$	67.22 (67.27)	4.23 (4.22)	19.60 (19.69)
4e	*p*-Cl	312	73	$C_{19}H_{12}O_2N_5Cl$	60.41 (60.36)	3.20 (3.14)	18.54 (18.48)
4f	*m*-Cl	310	70	$C_{19}H_{12}O_2N_5Cl$	60.41 (60.50)	3.20 (3.12)	18.54 (18.48)
4g	*p*-Br	314	61	$C_{19}H_{12}O_2N_5Br$	54.04 (54.11)	2.86 (2.77)	16.59 (16.64)

Fused tetracyclic quinazolin-4(3H)one (4a). A mixture of **3a** (2.91 gm, 0.01 mole), ethylacetoacetate (12.7 cm^3, 0.01 mole) and glacial acetic acid (20 mL) was refluxed for 4 h. The solution was concentrated, cooled, and the crude product obtained was recrystallized from chloroform:*n*-hexane (50% v/v) mixture, yield, 2.570 gm (72%), m.p. 310°C. IR: 1725–1690 broad, 1662 cm^{-1}, 1625. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.44 (s, 3H, Ar—CH_3), 2.47 (s, 3H, Ar—CH_3), 6.21 (s, 1H, =CH), 7.2–8.4 (m, 8H, Ar—H); ms: m/z 373(45), 342(55), 266(100), 107(35), 31(15). *Anal. Calcd.* for $C_{20}H_{15}O_2N_5$ (357): C, 64.34%; H, 4.05%; N, 18.76%. Found: C, 64.27%; H, 4.11%; N, 18.79%.

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