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A Facile Microwave Assisted One-pot Strategy for the Synthesis of Bis-hexahydroquinazolin-5(6H)-ones

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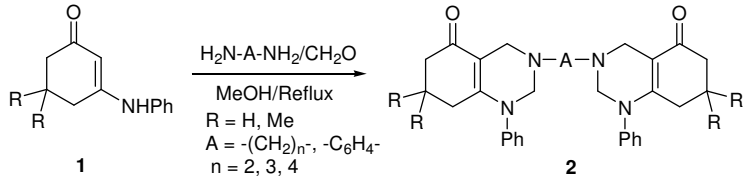
Abstract: A facile microwave assisted one-pot synthetic protocol has been devised for the synthesis of 3,3′-(alkanediyl) bis (1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-ones (**2a-c**), 3,3′-(1,4-phenylene) bis (1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2d**),3,3′-(alkanediyl) bis (7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-ones (**2e-g**) and 3,3′-(1,4-phenylene) bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2h**) by the cyclocondensation of cyclic enaminones **1a, b** with diamines and formaldehyde.

Keywords: Enaminones, Quinazolinones, Diamines, Cyclocondensation.

Introduction

Fused pyrimidines are found in a broad variety of natural products[1], used in medicines[2], possess antimalarial activities[3] and other important biological properties[4]. Recently, 1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione derivatives have been reported to exhibit potent calcium antagonist activities[5,6] and have also attracted considerable attention owing to their potential antibacterial activity against *Staphylococcus aureus, Escherichia coli*, *Pseudomonas aeruginosa*[7,8]. However, synthesis of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines[9] is least attended to and to the best of our knowledge bis(5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines) are unknown in the literature and hence their biological properties remain unexplored. Prompted by the promising biological properties of 1,2,3,4,5,6,7,8-octahydroquinazolines, we have recently reported[10] a facile synthetic methodology for 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines. In continuation with our efforts on the synthesis of tetrahydropyrimidines[11-14], we now report herein a facile

one pot synthetic strategy for bis-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-ones in which the two quinazoline rings are linked through flexible aliphatic chains or through rigid aromatic ring (Scheme 1).



Scheme 1

Experimental

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High resolution ^{1}H NMR and ^{13}C NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and *m*-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument. Microwave irradiation was carried out in a domestic MW oven (Samsung CE2733G) operating at 2450 MHz. Enaminones **1a** and **1b** were synthesized by our reported procedure[15].

General procedure

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% solution) in 1.5 mL methanol was shaken at room temperature for 5 minutes. To this a solution of enaminones **1** (1 mmol) was added in 5-6 mL methanol and the resulting mixture was irradiated in a domestic microwave oven for specified period of time (Table 2). After the completion of the reaction (monitored by TLC), methanol was removed under reduced pressure to give a gum, which on trituration with hexane and subsequent recrystallization in appropriate solvent gave compounds **2a**, **2e**, **2g** and **2h.** In case of compounds **2b, 2c, 2d** and **2f** the gum was chromatographed using neutral alumina and ethylacetate (eluant). Under thermal conditions these reactions took much longer time for completion giving the desired products in comparatively lower yields.

*3,3′-(Ethane-1,2-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2a**)*

It was obtained as a pale yellow solid in 85% yield; mp 182-184 ^{0}C (EtOAc); IR (KBr): 1493, 1566 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 4H, 2 CH_2), 2.12-2.28 (t, 4H, 2 CH_2), 2.31-2.60 (t, 4H, 2 CH_2), 2.83 (s, 4H, 2 CH_2), 3.73 (s, 4H, 2 CH_2), 4.43 (s, 4H, 2 CH_2), 7.07-7.87 (m, 10H); MS: m/z 483 (MH^+). Anal. Calc. for $C_{30}H_{34}N_4O_2$ (482.27): C, 74.66; H, 7.10; N, 11.61. Found: C, 74.41; H, 7.07; N, 11.66%.

*3,3′-(Propane-1,3-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2b**)*

It was obtained as yellow gum in 76% yield; IR (CCl_4): 1493, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.84-1.85 (m, 4H, 2 CH_2), 1.86-1.88 (m, 2H), 2.18-2.20 (t, 4H, 2 CH_2), 2.32-2.36 (t, 4H, 2 CH_2), 2.67-2.72 (t, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 4.30 (s, 4H, 2 CH_2), 7.11-7.13 (m, 4H), 7.27-7.43 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 22.10, 26.07, 27.72, 36.55, 47.96, 50.95, 71.98, 104.83, 127.36, 127.50, 129.84, 143,02, 158.36, 194.94; MS: m/z, 497 (MH^+). Anal. Calc. for $C_{31}H_{36}N_4O_2$ (496.28): C, 74.97; H, 7.31; N, 11.28. Found: C, 74.66; H, 7.33; N, 11.24%.

*3,3′-(Butane-1,4-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2c**)*

It was obtained as yellow gum in 77% yield; IR (CCl_4): 1493, 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (m, 4H, 2 CH_2), 1.85-1.88 (m, 4H, 2 CH_2), 2.21 (t, 4H, 2 CH_2), 2.33 (t, 4H, 2 CH_2), 2.62 (t, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 4.29 (s, 4H, 2 CH_2), 7.12-7.14 (m, 4H), 7.30-7.43 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 22.08, 25.59, 27.71, 30.51, 47.59, 52.59, 72.19, 104.76, 124.61, 127.37, 129.31, 143,05, 158.48, 195.03; MS: m/z, 511 (MH^+). Anal. Calc. for $C_{32}H_{38}N_4O_2$ (510.29): C, 75.26; H, 7.50; N, 10.97. Found: C, 75.50; H, 7.48; N, 10.92%.

*3,3′-(1,4-Phenylene)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2d**)*

It was obtained as yellow solid in 79% yield; mp 191-193 ^0C; IR (KBr): 1427, 1507, 1566 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.70-2.06 (m, 4H, 2 CH_2), 2.10-2.30 (t, 4H, 2 CH_2), 2.33-2.60 (t, 4H, 2 CH_2), 4.56 (s, 4H, 2 CH_2), 4.99 (s, 4H, 2 CH_2), 6.96-7.93 (m, 14H); MS: m/z, 531 (MH^+). Anal. Calc. for $C_{34}H_{34}N_4O_2$ (530.27): C, 76.95; H, 6.46; N, 10.56. Found: C, 76.70; H, 6.45; N, 10.51%.

*3,3′-(Ethane-1,2-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2e**)*

It was obtained as yellow solid in 87% yield; mp 193-194 ^0C ($CHCl_3$/Hexane); IR (KBr): 1493, 1566, 1619 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (s, 12H, 4 CH_3), 2.10 (s, 4H, 2 CH_2), 2.23 (s, 4H, 2 CH_2), 2.93 (s, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 4.50 (s, 4H, 2 CH_2), 7.03-7.76 (m, 10H); MS: m/z, 539 (MH^+). Anal. Calc. for $C_{34}H_{42}N_4O_2$ (538.33): C, 75.80; H, 7.86; N, 10.40. Found: C, 76.05; H, 7.88; N, 10.44%.

*3,3′-(Propane-1,3-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2f**)*

It was obtained as yellow gum in 75% yield; IR (CCl_4): 1427, 1493, 1566, cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (s, 12H, 4 CH_3), 1.59-1.61 (m, 2H), 1.99 (s, 4H, 2 CH_2), 2.13 (s, 4H, 2 CH_2), 2.60-2.65 (m, 4H, 2 CH_2) 3.58 (s, 4H, 2 CH_2), 4.24 (s, 4H, 2 CH_2), 7.01-7.08 (m, 4H), 7.25-7.41 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 24.92, 27.28, 27.36, 31.64, 39.99, 46.40, 48.65, 48.96, 49.46, 70.92, 102.15, 126.38, 127.89, 129.39, 141.78, 155.62, 193.42. Anal. Calc. for $C_{35}H_{44}N_4O_2$ (552.35): C, 76.05; H, 8.02; N, 10.15. Found: C, 76.31; H, 7.98; N, 10.11%.

*3,3′-(Butane-1,4-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2g**)*

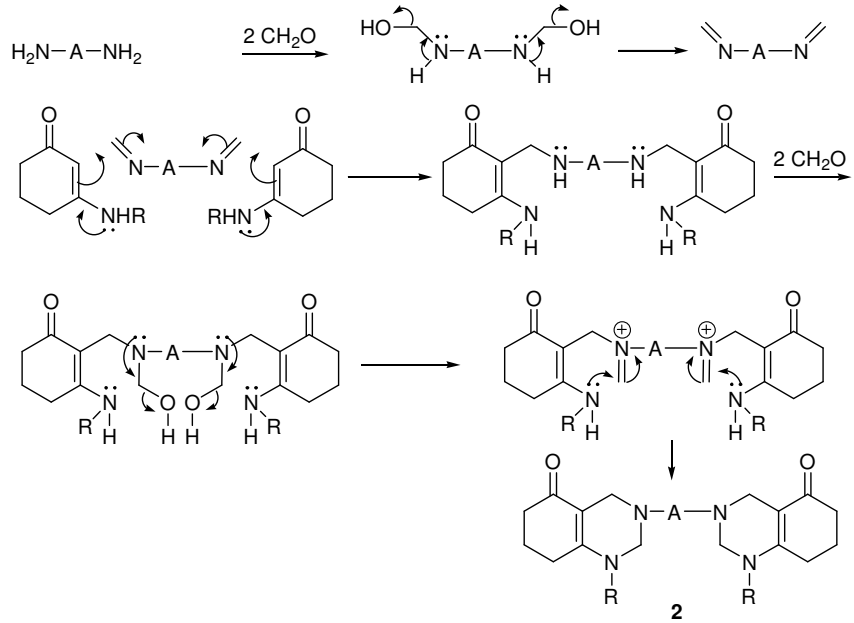
It was obtained as a pale yellow solid in 90% yield; mp 168-169 ^0C (EtOAc); IR (KBr): 1440, 1566, 1613 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (s, 12H, 4 CH_3), 1.46-1.83 (m, 4H, 2 CH_2), 2.13 (s, 4H, 2 CH_2), 2.26 (s, 4H, 2 CH_2), 2.56-2.90 (m, 4H, 2 CH_2) 3.76 (s, 4H, 2 CH_2), 4.45 (s, 4H, 2 CH_2), 7.10-7.86 (m, 10H); MS: m/z, 567 (MH^+). Anal. Calc. for $C_{36}H_{46}N_4O_2$ (566.36): C, 76.29; H, 8.18; N, 9.89. Found: C, 76.02; H, 8.21; N, 9.83%.

*3,3′-(1,4-Phenylene)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2h**)*

It was obtained as yellow solid in 89% yield; mp 126-128 ^0C (MeOH/EtOAc); IR (KBr): 1507, 1566, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (s, 12H, 4 CH_3), 2.00 (s, 4H, 2 CH_2), 2.23 (s, 4H, 2 CH_2), 4.27 (s, 4H, 2 CH_2), 4.89 (s, 4H, 2 CH_2), 6.91-6.96 (m, 8H), 7.27-7.36 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 28.08, 28.52, 32.82, 41.24, 45.96, 50.21, 52.59, 71.21, 104.63, 119.13, 127.53, 127.62, 129.88, 142.84, 157.52, 194.22; MS: m/z, 587 (MH^+). Anal. Calc. for $C_{38}H_{42}N_4O_2$ (586.33): C, 77.78; H, 7.21; N, 9.55. Found: C, 77.52; H, 7.18; N, 9.61%.

Results and Discussion

Thus, when a mixture of 3-anilinocyclohex-2-en-1-one (**1a**), ethylenediamine and formaldehyde (2:1:4) in methanol was subjected to MWI, work-up of the reaction mixture followed by chromatographic purification yielded a solid in 85% yields, which was characterized as 3,3′-(ethane-1,2-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (**2a**). The reaction was found to be general with other diamines and with corresponding **1a-b** to give the respective **2b-h** in 77-90% overall yields (Table 1). These reactions were also carried out under thermal conditions to give the expected products in comparatively lower yields and in addition they took much longer time for completion (Table 2). The structures of the Bis-quinazolines were assigned on the basis of spectral and analytical data. Thus, the infrared spectra of **2a-h** showed strong peaks in the range of 1427 to 1619 cm^{-1} due to highly delocalised double bonds and carbonyl group stretching frequencies of enaminone functionalities. In the ^1H NMR spectra of **2a** & **2e** the NCH_2 protons of ethylene chain appeared as singlets at 2.83 ppm and 2.93 ppm respectively whereas the NCH_2 protons of propylene chain in **2b** & **2f** gave triplets in the range of 2.60-2.72 ppm. The protons at C_2 of propylene chain gave multiplets in the range of 1.59-1.88 ppm. Likewise in **2c** & **2g** the protons at C_1 & C_2 of butylene chains gave multiplets in the range of 2.56-2.90 and 1.46-1.88 ppm respectively. The protons at C_2 and C_4 of quinazoline ring resonated in the range of 4.24-4.99 and 3.64-4.56 ppm respectively. In **2a-d** the C_8 protons of the parent ring appeared as triplets between 2.10 & 2.30 ppm but in **2e-h** they appeared as singlets between 1.99 & 2.10 ppm. The C_6 protons of the parent ring in **2a-d** appeared as triplets between 2.31 & 2.60 ppm but in **2e-h** they appeared as singlets between 2.13 & 2.26 ppm. The C_7 protons of the ring in **2a-d** resonated giving multiplets in the range of 1.58-2.06 ppm. The two-methyl protons at C_7 in **2e-h** gave singlets between 0.90 & 1.03 ppm. The aromatic protons resonated in their usual range of 6.91-7.93 ppm. A plausible mechanism for the formation of **2** from the cyclic enaminones **1** is worked out (Scheme 2).



Scheme 2.

Table 1. Synthesis of bis-quinazolinones **(2a-h)**

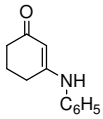
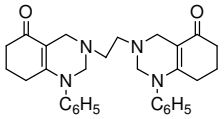
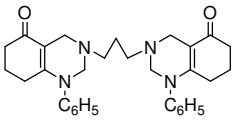
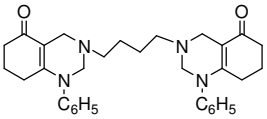
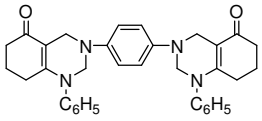
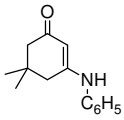
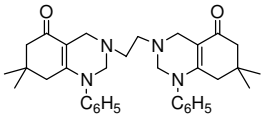
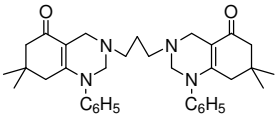
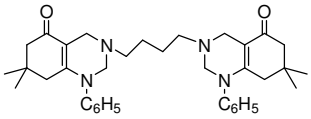
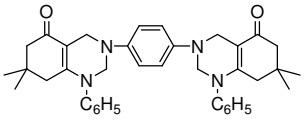
Entry	Enaminones (**1**)	Conditions	Bis-quinazolinones (**2**)
1	 **1a**	H_2N-$(CH_2)_2$-NH_2, CH_2O, MeOH/180 W 3 minutes	 **2a**
2	**1a**	H_2N-$(CH_2)_3$-NH_2, CH_2O, MeOH/180 W 2 minutes	 **2b**
3	**1a**	H_2N-$(CH_2)_4$-NH_2, CH_2O, MeOH/180 W 2.5 minutes	 **2c**
4	**1a**	H_2N-C_6H_4-NH_2, CH_2O, MeOH/180 W, 3 minutes	 **2d**
5	 **1b**	H_2N-$(CH_2)_2$-NH_2, CH_2O, MeOH/180 W, 2 minutes	 **2e**
6	**1b**	H_2N-$(CH_2)_3$-NH_2, CH_2O, MeOH/180 W, 4 minutes	 **2f**
7	**1b**	H_2N-$(CH_2)_4$-NH_2, CH_2O, MeOH/180 W, 1.5 minutes	 **2g**
8	**1b**	H_2N-C_6H_4-NH_2, CH_2O, MeOH/180 W, 2 minutes	 **2h**

Table 2. Comparison of microwave irradiation and thermal condition results**.**

Compound	Microwave Irradiation (180 W)		Thermal (Reflux)	
	Time, min	Yield, %	Time, h	Yield, %
2a	3	85	27	58
2b	2	76	22	70
2c	2.5	77	24	65
2d	3	79	24	71
2e	2	87	22	88
2f	4	75	23	68
2g	1.5	90	8	59
2h	2	89	20	55

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