Synthesis of some new 6-substituted quinazolino[4,3-*b*]quinazolin-8-ones under solvent-free conditions

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A facile and rapid synthesis of some new 6-substituted quinazolino[4,3-*b*]quinazolin-8-ones derivatives was investigated. The synthesis involved two-step condensation from isatoic anhydride. The products were obtained by condensation of 2-(*o*-aminophenyl)-4(3*H*)-quinazolinone and ortho-esters in the absence of organic or inorganic reagents in solvent-free conditions under microwave irradiation.

Keywords: 2-(*o*-aminophenyl)-4(3*H*)-quinazolinone; isatoic anhydride; microwave irradiation; *ortho*-esters; solvent-free conditions; 6-substituted quinazolino[4,3-*b*]quinazolin-8-ones

The quinazoline ring skeleton is a frequently encountered heterocycle in pharmacological literature. Among the most important effects are hypnotic, anticonvulsant,[1] muscle relaxant,[2] analgesic,[3] anti-inflammatory,[4] antibacterial activities[5] and as potent non-nucleoside reverse transcriptase inhibitors of human immunodeficiency virus (HIV-1).[6] Furthermore, these heterocyclic compounds were recently isolated from plant sources, for example, the pyrroloquinazolinoquinoline alkaloids, luotonin **A1** and **B2** [7] and the indolopyrido quinazolinone, rutaecarpin[8] **3** which are useful for their antitumor activity and hypertensive, diuretic and uterotonic properties (Fig. 1).

These useful compounds are prepared by various methods.[9] Recently, the synthesis of the quinazoline ring skeleton have been reported by the cyclocondensation of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline with isatoic anhydride,[10] by the condensation of 2-amino-*N*-benzimidazolyl benzamide with ortho-esters,[11] by the Niementowski reaction[12] and by the condensation of 2-(2-aminophenyl)indole with 2-cyanobenzothiazoles,[13] under microwave irradiation.

The microwave-assisted chemical transformations have become important, due to several advantages over conventional thermal reactions, and they have been used extensively for the rapid synthesis of variety of heterocyclic compounds.[14]

We have recently reported the preparation of quinazolinone derivatives from isatin-3-imines,[15a] by the three-component condensation reaction of isatoic anhydride, primary amine and urea or thiourea[15b] and isatoic anhydride with isatin-3-imine.[15c] Now, we report a rapid and efficient procedure for microwave-assisted preparation of some novel tetracyclic 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones derivatives.

Synthesis of 2-(*o*-aminophenyl)-4 (3*H*)-quinazolinone 4

The preparation of 2-(*o*-aminophenyl)-4(3*H*)-quinazolinone 4 involved a Niementowski modification of the Freidlander synthesis.[16] In the reaction between isatoic anhydride 7 and anthranilamide 8, the nucleophilic attack is provided by the *o*-amino group and not the carbamoyl group of the anthranilamide, to give an intermediate 9 which must be treated with aqueous sodium carbonate to form 2-(*o*-aminophenyl)-4 (3*H*)-quinazolinone 4 (Scheme 1).

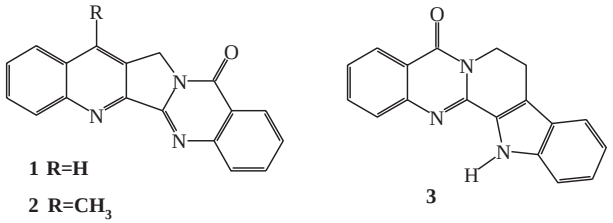


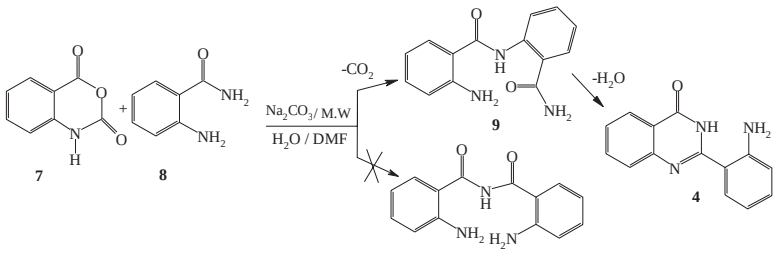
Fig. 1

Synthesis of 8*H*-quinazolino[4,3-*b*]quinazolin-8-one derivatives

Recently, the preparation of the 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones has been reported, by fusing the quinazolinone ring and anthranilic acid under microwave irradiation, but, only compound **6a** (Table 1) has been described (30 min, adsorbed on graphite, 79% or 10 min, using CH_3CO_2H as catalyst, 82%).[17] However, we have found that the condensation of 2-(*o*-aminophenyl)-4(3*H*)-quinazolinone **4** and ortho-ester **5a** results in rapid formation of the 8*H*-quinazolino[4,3-*b*]quinazolin-8-one **6a** (97%) in the absence of organic or inorganic reagents in solvent-free conditions (Table 1, Scheme 2).

Prompted by this success, we extended the reaction of quinazolinone **4** with a range of other ortho-esters **5b–f**, under similar conditions, furnishing the respective 6-substituted quinazolino[4,3-*b*]quinazolin-8-ones in good to excellent yields. The reaction was performed in open vessels in a microwave oven. The results are summarised in Table 1.

In summary, we have described a successful strategy, for the preparation of new polyheterocyclic compounds 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones in the absence of catalyst and under solvent-free conditions. The method offers several advantages including high yield of products, cleaner reaction



Scheme 1

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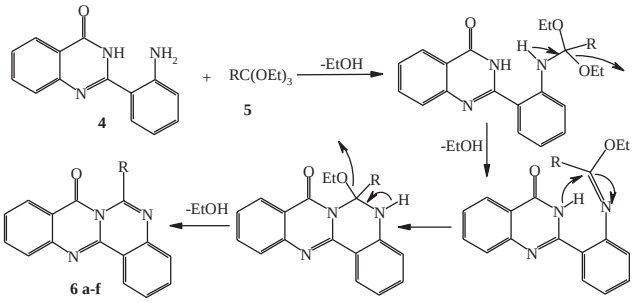

Scheme 2

profiles, short reaction times, simple experimental work up procedure, which make it a useful process for the synthesis of 6-substituted quinazolino[4,3-*b*]quinazolin-8-ones. In connection with recently published results on the utility of microwaves in multistep organic synthesis, this work confirms that reaction mixtures exposed to microwaves allow an easy, a rapid and access to key heterocycles with potential pharmaceutical value.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were measured on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determind on a Bruker 500 DRX AVNCE instrument at 500 and 125 MHz, respectively. Mass spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O rapid analyzer. Microwave irradiation were carried out in a National oven, model 5250, at 2450 MHz.

General procedure

Synthesis of 2-(o-aminophenyl)-4(3H)-quinazolinone **(4)**: A mixture of isatoic anhydride **7** (2.45 mmol, 0.4 g), 2-aminobenzamide **8** (2.45 mmol, 0.33 g), Na_2CO_3 (0.1 g), H_2O (1 ml) and *N,N*- dimethylformamide (3 ml) was placed in a tall beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for 10 min with a power of 385 W. Then the reaction mixture was allowed to cool to room temperature. A mixture of water/ice (10 ml) was added and the solid precipitate was collected by filtration, dried and recrystallised from ethanol (96%) to afford a pure product.

2-(o-Aminophenyl)-4(3H)-quinazolinone **(4):**[16] Yield 85%, M.p. 239–241 °C, IR(KBr), (ν_{max} /cm^{-1}): 3330, 3145, 3035, 2830, 1664 (C=O). MS : *m*/*z*, (%)= 237(M$^+$, 80), 162(75), 119(100), 91(85), 64(40), 53(25).

Synthesis of 6-substituted quinazolino[4,3-b]quinazolin-8-ones **(6)**: A mixture of 2-(*o*-aminophenyl)-4(3*H*)-quinazolinone **4** (0.5 mmol, 0.118 g) and ortho-esters **5a–f** (1.5 ml) in a tall beaker was placed in the microwave oven, the beaker was covered with a stemless funnel and irradiated with power and time as indicated in Table 1. After completion of the reaction, pure products were obtained similar to those described in the procedure for compound **4**.

Quinazolino[4,3-b]quinazolin-8-one **(6a)**.[17,18] White crystalline solid, yield 97%, M.p.: 197–198 °C, IR(KBr), (ν_{max} /cm^{-1}): 1700 (C=O), ^{1}H NMR (CDCl $_3$) δ_H: 7.57(t, *J*=6.5 Hz, 1H), 7.69(t, *J*=6.9 Hz, 1H), 7.80–7.94(m, 4H), 8.48(d, *J*=7.7 Hz, 1H), 8.88(d, *J*=7.7 Hz, 1H), 9.49(s,1H) ppm. ^{13}C NMR ($CDCl_3$) d_C: 119.19, 121.91, 126.37. 127.05, 128.02, 128.23, 128.62, 129.43, 134.17, 136.40, 138.24, 143.55, 144.92 and 148.10 (14C, aromatic carbons), 159.72 (1C, C=O) ppm. MS : *m*/*z*, (%)= 247(M$^+$, 100), 219(50), 129(25), 102(50), 76(50), 63(50), 50(60).

6-Methylquinazolino[4,3-b]quinazolin-8-one **(6b)**:[19] White crystalline solid, yield 99%, M.p.: 180–181°C, IR(KBr), (ν_{max} /cm^{-1}): 1693 (C=O), ^{1}H NMR (CDCl $_3$) δ_H: 3.12(s, 3H, Me), 7.50(t, *J*=7.1 Hz, 1H), 7.56 (t, *J*=7.4 Hz, 1H), 7.66(d, *J*=7.8 Hz, 1H), 7.74(t, *J*=7.1 Hz, 1H), 7.83 (d, *J*=8.0 Hz, 1H), 7.86(t, *J*=7.9 Hz, 1H), 8.35(d, *J*=8.0 Hz, 1H), 8.73 (d, *J*=7.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) d_C: 27.83(1C, CH_3), 120.92, 121.77, 126.38, 126.66, 127.17, 127.36, 127.75, 128.26, 133.75, 135.66, 142.42, 146.33, 146.86 and 150.71, (14C, aromatic carbons), 161.69 (1C, C=O) ppm. MS : *m*/*z*, (%)= 261(M$^+$, 100), 102(40), 90(35), 75(40), 63(40), 50(55).

6-Ethylquinazolino[4,3-b]quinazolin-8-one **(6c)**:[19] White crystalline solid, yield 98%, M.p. 156–157 °C, IR(KBr), (ν_{max} /cm^{-1}): 1708 (C=O),

Table 1 The reaction of 2-(*o*-aminophenyl)-4(3*H*)-quinazolinone with *ortho*-esters

Product	R	Time /min	Yield/%[a, b]	M.p./°C	Lit. m.p/°C
6a	H	4	97	197–198	19817, 19718
6b	Me	3	99	180–181	178.5–179.519
6c	Et	3	98	156–157	155–15619
6d	n-Pr	4.5	97	129–131	Novel
6e	n-Bu	4.5	97	118–120	Novel
6f	Ph	5	95	291–292	29220

[a]Irradiation conditions were P/ W 385.
[b]Yield of pure isolated product based on 2-(*o*-aminophenyl)-4 (3*H*)-quinazolinone.

^{1}H NMR (CDCl $_3$) δ_H: 1.43(t, *J*=7.2 Hz, 3H, CH_3), 3.52(q, *J*=7.2 Hz, 2H, CH_2), 7.48(t, *J*=6.9 Hz, 1H), 7.54(t, *J*=7.9 Hz, 1H), 7.69(d, *J*=7.0 Hz, 1H), 7.71(t, *J*=7.0 Hz, 1H), 7.77(d, *J*=7.2 Hz, 1H), 7.83(t, *J*=7.9 Hz, 1H), 8.34(d, *J*=7.9 Hz, 1H), 8.71(d, *J*=7.8 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) d_C: 12.87(1C, CH_3), 32.40(1C, CH_2), 121.12, 121.75, 126.40, 126.62, 127.31, 127.41, 127.76, 128.24, 133.70, 135.60, 142.45, 146.61, 146.90 and 154.94(14C, aromatic carbons), 161.68(1C, C=O) ppm. MS : *m*/*z*, (%)= 274(M$^+$, 100), 260(30), 119(20), 102(30), 90(30), 76(40), 63(40), 50(50).

6-Propylquinazolino[4,3-b]quinazolin-8-one **(6d)**: White crystalline solid, yield 97%, M.p. 129–131 °C, IR(KBr), (ν_{max} /cm^{-1}): 1698 (C=O), ^{1}H NMR (CDCl $_3$) δ_H: 1.06(t, *J*=7.3 Hz, 3H, CH_3), 1.89(m, 2H, CH_2), 3.47(t, *J*=7.6 Hz, 2H, CH_2), 7.52(t, *J*=6.9 Hz, 1H), 7.57(t, *J*=7.8 Hz, 1H), 7.71(d, *J*=7.5 Hz, 1H), 7.75(t, *J*=7.9 Hz, 1H), 7.81(d, *J*=7.7 Hz, 1H), 7.86(t, *J*=7.5 Hz, 1H), 8.38(d, *J*=7.6 Hz, 1H), 8.76(d, *J*=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) d_C: 14.43(1C, CH_3), 21.97(1C, CH_2), 40.79(1C, CH_2), 121.18, 121.84, 126.47, 126.70, 127.37, 127.47, 127.84, 128.33, 133.80, 135.70, 142.48, 146.72, 147.01 and 154.94(14C, aromatic carbons), 161.11(1C, C=O) ppm. MS : *m*/*z*, (%)= 289(M$^+$, 100), 274(80), 261(75), 119(30), 102(35), 90(30), 76(45), 63(45), 50(50). Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. found: C, 74.68; H, 5.11; N, 14.44.

6-Butylquinazolino[4,3-b]quinazolin-8-one **(6e):** White crystalline solid, yield 97%, M.p. 118–120 °C, IR(KBr), (ν_{max} /cm^{-1}): 1707 (C=O), ^{1}H NMR (CDCl $_3$) δ_H: 0.99(t, *J*=7.3 Hz, 3H, CH_3), 1.50(m, 2H, CH_2), 1.83(m, 2H, CH_2), 3.44(t, *J*=7.7 Hz, 2H, CH_2), 7.43 (t, *J*=7.75 Hz, 1H), 7.48(t, *J*=7.3 Hz, 1H), 7.63(d, *J*=7.7 Hz, 1H), 7.67(t, *J*=7.5 Hz, 1H), 7.72(d, *J*=8.0 Hz, 1H), 7.77(t, *J*=7.2 Hz, 1H), 8.29(d, *J*=7.9 Hz, 1H), 8.64(d, *J*=7.9 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) d_C: 14.60(1C, CH_3), 23.10(1C, CH_2), 30.68(1C, CH_2), 38.75(1C, CH_2), 121.11, 121.75, 126.40, 128.59, 127.31, 127.37, 127.78, 128.20, 133.68, 135.58, 142.42, 146.61, 146.88 and 154.09(14C, aromatic carbons), 161.64(1C, C=O) ppm. MS : *m*/*z*, (%)= 303(M$^+$, 30), 274(60), 261(100), 119(15), 102(25), 90(25), 76(30), 63(25), 50(25), 41(35). Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. found: C, 75.19; H, 5.61; N, 13.78.

6-Phenylquinazolino[4,3-b]quinazolin-8-one **(6f)**:[20] White crystalline solid, yield 95%, M.p. 291–292 °C, IR(KBr), (ν_{max} /cm^{-1}): 1684 (C=O), ^{1}H NMR (CDCl $_3$) δ_H: 7.32(d, *J*=6.9 Hz, 1H), 7.63–7.57(m, 5H), 7.72 (d, *J*=8.0 Hz, 1H), 7.89(t, *J*=7.3 Hz, 1H), 7.95–7.99(m, 3H), 8.19 (d, *J*=7.2 Hz, 1H), 8.53(d, *J*=7.8 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) d_C: 121.21, 122.75, 125.51, 126.41, 127.17, 127.22, 127.25, 127.68, 128.47, 128.82, 129.91, 130.62, 132.23, 133.87, 151.64, 153.09, 154.34 and 155.08(18C, aromatic carbons), 163.57(1C, C=O) ppm. MS : *m*/*z*, (%)= 323(M$^+$, 100), 263(70), 102(50), 90(45), 75(60), 63(550), 50(40).

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University and Professor A. Khodai for helpful suggestions.

Received 14 February 2004; accepted 13 May 2004
Paper 04/2368

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