One-pot Synthesis of Substituted Quinazolin-4(3*H*)-ones under Microwave Irradiation†

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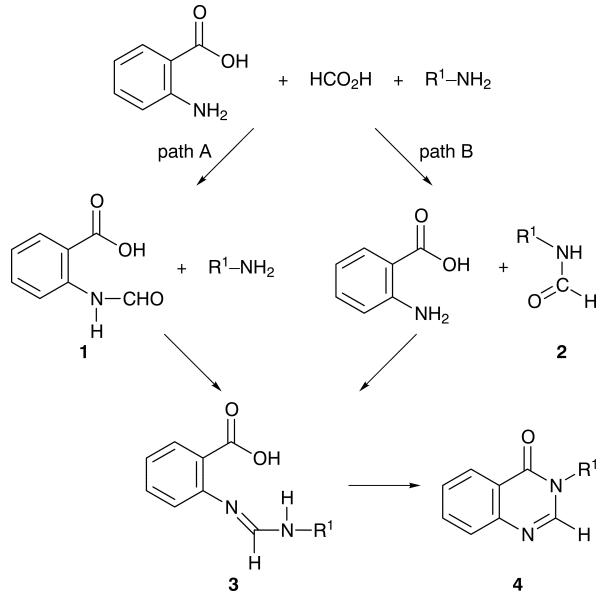
Synthesis of the title compounds by cyclocondensation of anthranilic acid, formic acid (or orthoesters) and an amine in one pot under microwave irradiation takes place in a few minutes.

Preparations of quinazolin-4(3*H*)-ones are in demand because of their potential biological and pharmaceutical activities.[1] Synthesis of these compounds by one-pot reaction of anthranilic acid with an amine and formic acid, as two separate synthons for N-3 and C-2 in the quinazolin-4(3*H*)-one ring system, has not been reported. We wish to report here a facile synthesis of substituted quinazolin-4(3*H*)-ones in fairly high yields by three-component cyclocondensation under microwave irradiation.



Scheme 1

A mixture of the reactants was irradiated under conditions described in Table 1 in the absence of solvent or any dehydrating agents.[2] In order to control the reaction, the irradiation was carried out in two stages (t_1 and t_2) with a cooling time between them. In both cases, however, to ensure optimum yields of products, an excess of formic acid had to be employed. The reaction can proceed *via* two pathways, namely A and B (Scheme 1). Path A involves *N*-formylation of anthranilic acid, condensation of the resultant 2-formamidobenzoic acid **1** with the amine and then intramolecular amidation of the intermediate amidine **3**. On the other hand, the amine instead of anthranilic acid may be formylated and so the reaction would go through the known Niementowski reaction (path B). When the reactions of 2-formamidobenzoic acid **1** with aniline[3] and the condensation of formanilide **2** with anthranilic acid[4] were conducted under microwave irradiation, the desired 3-phenylquinazolin-4(3*H*)-one **4a** was obtained in a few minutes. Thus, the *N*-formylation step occurs very quickly, and during the short reaction time. Attempts to use CH_3CO_2H instead of HCO_2H were not successful. The success of the reaction with HCO_2H can be ascribed to the intermediate formation of *N*-formyl derivatives that form more readily than other *N*-acyl derivatives.

Using orthoesters with a catalytic amount of toluene-*p*-sulfonic acid instead of formic acid in the above reaction leads to the formation of 2,3-disubstituted quinazolin-4(3*H*)-ones **6** in fairly high yields (Table 1). The reaction occurs in a much reduced time with respect to conventional refluxing method.[5] Recently, it was reported that 2-substituted-3,1-benzoxazin-4-ones are obtained from microwave promoted reaction of orthoesters with anthranilic acid in a few minutes and high yields.[6] Thus, by considering that 3,1-benzoxazin-4-ones are very prone to react with amines,[7] the intermediacy of these compounds in this one-pot synthesis is probable. However, the intermediacy of amidines **5** in these reactions cannot be ruled out (Scheme 2).[5,8,11]

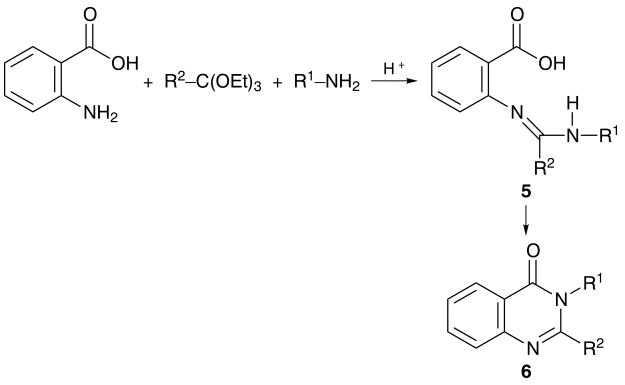
All the products **4a**–**f** and **6a**–**c** are known and were characterized by mp, IR, ^{1}H and ^{13}C NMR spectral analyses.[14]

In conclusion we have introduced a simple method for preparing (2),3-(di)substituted quinazolin-4(3*H*)-ones in a few minutes and high yields by microwave irradiation of simple starting materials in one pot.

Experimental

Melting points are uncorrected. Infrared spectra were obtained in KBr wafers on a Shimadzu IR-470 spectrometer. NMR spectra were recorded on a JEOL-EX-90 spectrometer at 90 and 22.63 MHz for ^{1}H and ^{13}C, respectively. *J* values are given in Hz. Microwave irradiation was carried out in a National oven, Model 5250 at 2450 MHz. All the experiments were performed in an efficient hood, in order to avoid contact with vapors.

General Procedure for Preparation of Compounds **4a**–**f**.—A mixture of anthranilic acid (1.37 g, 10 mmol), formic acid (0.69 g, 15 mmol) and the amine (13 mmol for liquids or 10 mmol for solids) contained in a tall beaker was placed in the microwave oven and the beaker was covered with a stemless funnel and irradiated for time t_1 at power p_1 (Table 1). After about 5 min, as it cooled to room temperature, the reaction mixture was irradiated again for t_2 at p_2. Then the reaction mixture was dissolved in hot ethanol–water from which products crystallized. Use of 1 M NaOH–ethanol (2:5)



Scheme 2

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research* (*S*), 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research* (*M*).

Table 1 Melting points and irradiation conditions

Product	R^1	R^2	Irradiation conditions				Yield (%)[a]	Mp/°C	Lit. mp/°C
			t_1/min	p_1/W	t_2/min	p_2/W			
4a	Ph	—	3	210	4	385	76	139–140	138–139[b]
4b	$PhCH_2$	—	3	210	6	385	68	119–120	117–118[b]
4c	4-ClC_6H_4	—	3	210	3	385	73	182–183	180–181[c]
4d	4-MeC_6H_4	—	3	210	3	385	72	146–147	148–149[d]
4e	4-EtC_6H_4	—	3	210	3	385	84	130–131	126–128[e]
4f	3,4-$Me_2C_6H_3$	—	3	210	3	385	87	134.5–135.5	135[f]
6a	Ph	Ph	5	385	1	490	79	159–160	158–159[g]
6b	$PhCH_2$	Ph	5	385	2	490	81	138–139	137–139[g]
6c	Ph	Me	5	385	1	490	89	147–149	147–148[h]

[a]Yield of pure isolated product based on anthranilic acid. [b]Ref. 12. [c]Ref. 8. [d]Ref. 13. [e]Ref. 9. [f]Ref. 3. [g]Ref. 10. [h]Ref. 11.

as crystallization solvent accelerates the crystallization with a slight decrease in yield. Products before analysis were recrystallized from 95% ethanol.

Selected Data for **4f**.—Colorless needles, ν_{max} (KBr)/cm^{-1} 1699 (C=O), 1598, 1463 (pyrimidine ring); δ_H ($CDCl_3$) 8.36 (1 H, dd, *J* 7.7 and 0.7, 5-H), 8.11 (1 H, s, 2-H), 7.05–7.85 (6 H, m, 6-, 7-, 8-H and Ar), 2.3 (6 H, s, 2 Me); δ_C [$(CD_3)_2SO$] 160.07 (C-4), 147.74 (C-2), 147.25 (C-8a), 137.39 (C-1′), 137.15 (C-7), 135.23, 134.62 (C-3′ and -4′), 121.92 (C-4a), 124.56, 126.44, 127.33, 127.41, 128.11, 130.10 (6 CH), 19.34 and 19.06 (2 Me).

Alternative Procedures for Preparation of **4a**.—A mixture of 2-formamidobenzoic acid[7] **1** (1.65 g, 10 mmol) and aniline (1.21 g, 13 mmol) contained in a tall beaker was covered with a stemless funnel and irradiated for 6 min at 385 W. After cooling, the resultant red–brown residue was crystallized from hot ethanol–water, yielding 1.57 g (71%) of **4a** (path A). In order to verify the viability of path B under the above condition, a mixture of formanilide **2a** (1.21 g, 10 mmol), anthranilic acid (1.37 g, 10 mmol) and a few drops of *N*,*N*-dimethylacetamide, as fusion accelerator, were irradiated as above. The resultant residue after crystallization from hot ethanol–water gave 1.81 g (83%) of **4a**.

General Procedure for Preparation of Compounds **6a**–**c**.—A mixture of anthranilic acid (1.37 g, 10 mmol), triethyl orthoacetate or triethyl orthobenzoate (20 mmol) and the amine (13 mmol) with a catalytic amount of toluene-*p*-sulfonic acid (PTSA) contained in a tall beaker was placed in the microwave oven and covered with a stemless funnel. The beaker was irradiated for 5 min at 385 W and then for 1–2 min at 490 W. The resultant residues were crystallized from ethanol–water or ethanol–1 M NaOH (5:2 v/v). The separated crystals were further recrystallized from 95% ethanol.

Selected Data for **6a**.—Colorless needles, ν_{max} (KBr)/cm^{-1} 1679 (C=O), 1599, 1583, 1463 (pyrimidine ring); δ_H ($CDCl_3$) 8.36 (1 H, ddd, *J* 7.8, 1.5 and 0.5, 5-H), 7.70–7.90 (2 H, m, 7-, 8-H), 7.05–7.65 (11 H, m, 6-H and 2 Ph); δ_C [$(CD_3)_2SO$] 161.50 (C-4), 155.27 (C-2), 147.33 (C-8a), 135.68, 134.87 (C-1′ and -1″), 137.88, 129.57, 128.97, 128.85, 128.68, 128.27, 127.58, 127.50, 127.30 (9 CH), 126.56 (C-5), 120.78 (C-4a).

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