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.



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 $(t_1 \text{ and } t_2)$ 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 aniline³ and the condensation of formanilide 2 with anthranilic $acid^4$ were conducted under microwave irradiation, the desired 3-phenylquinazolin-4(3H)-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(3H)-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 2substituted-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, ¹H and ¹³C NMR spectral analyses.¹⁴

In conclusion we have introduced a simple method for preparing (2),3-(di)substituted quinazolin-4(3H)-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 ¹H and ¹³C, 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)



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Table 1Melting points and irradiation conditions

Product	R ¹	R ²	Irradiation conditions						
			t ₁ /min	p_1/W	t ₂ /min	p_2/W	Yield (%) ^a	Mp/°C	Lit. mp/°C
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-CIC ₆ H₄		3	210	3	385	73	182–183	180–181 [°]
4d	4-MeČ ₆ H₄		3	210	3	385	72	146–147	148–149 ^d
4e	4-EtC ₆ H ₄		3	210	3	385	84	130–131	126–128 ^e
4f	3,4-Me ₂ C ₆ H ₃		3	210	3	385	87	134.5–135.5	135 ^ŕ
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 ^{<i>h</i>}

^aYield of pure isolated product based on anthranilic acid. ^bRef. 12. ^cRef. 8. ^dRef. 13. ^eRef. 9. ^fRef. 3. ^gRef. 10. ^hRef. 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); $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ [(CD₃)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 acid⁷ 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); $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ [(CD₃)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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