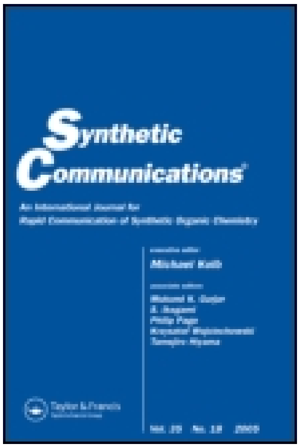

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Convergent One-Pot Synthesis of 3-Substituted Quinazolin-4(3H)-ones under Solvent-Free Conditions

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Abstract: A convenient method for the synthesis of 3-substituted quinazolin-4(3H)-ones using the convergent reactions of formic acid, a primary amine, and isatoic anhydride under solvent-free conditions and with brief microwave irradiation is described.

Keywords: Formic acid, isatoic anhydride, microwave, quinazolin-4(3H)-one, solvent-free

Natural and synthetic molecules with the core of quinazoline ring system show a wide range of biological activities.[1–5] The chemotherapeutic use of quinazoline alkaloids may date back to the ancient Chinese treatment of malaria with the herbal preparations from *Dichroa febrifuja*.[6] At the present, some synthetic quinazoline-based drugs such as metolazone, quinethazone, and prazosin have achieved medicinal approval for their unique pharmacological indices, and many others are under clinical evaluation.[7,8] As a consequence of these important properties, many approaches into the quinazoline ring systems were developed over the past decades[9] and are still pursued as a result of new emerging methods, such as microwave heating.[10–12] Performing reactions under microwave irradiation frequently gives rise to some rate enhancement and improvement of yields. Perhaps the prominent feature of

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most microwave conditions is the in situ quick conversion of microwaves to heat and the possible more homogeneous thermal profile than conventional heating methods.[13,14] In many such cases, the role of solvents as heat dispersants are no longer needed. The so-called solvent-free reactions are eco-friendly and, in view of greenchemistry's desire for avoiding the solvent hazards, are in demand.

The context of our interest in multicomponent condensations to quinazoline derivatives[15,16] led us to test the reaction of isatoic anhydride, formic acid, and a primary amine under solvent-free and microwave conditions. Herein, we report that under such conditions these simple starting materials quickly react with each other to provide 3-substituted quinazolin-4(3H)-ones **3** in fairly high yields (see Table 1).

To our knowledge, there has been no report of the one-pot synthesis of these products using formic acid and primary amines, as two separate synthons for C-2 and N-3, in cyclocondensation with isatoic anhydride.

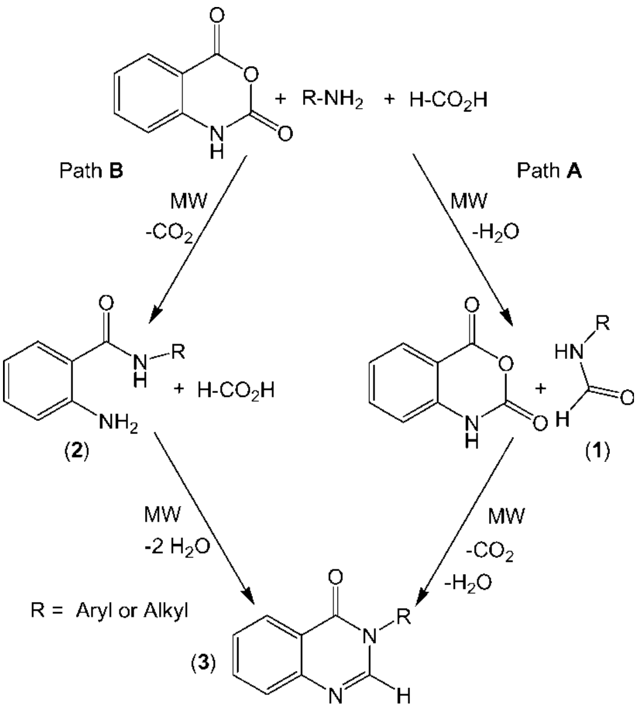
The mechanism of reaction can be rationalized in terms of two involved pathways, namely A and B. As is depicted in Scheme 1, these pathways ultimately converge on the synthesis of the same products. In path A, the primary amine reacts with formic acid to produce the formanilide **1**, which would subsequently condense with isatoic anhydride to yield the product **3**. The validity of this path clearly depends on the viability of its two steps under the reaction conditions. To verify the formation of formanilides **1** and thus confirm their participation in the course of reaction, we submitted a solvent-free mixture of formic acid and an appropriate primary amine to microwave irradiation for the comparable time. The results are shown in Table 2 and imply the rapid formation of formanilides **1** in good yields as well as clearly suggest their intermediacy in the synthesis of **3**. Our examination concerning the condensation of formanilides with isatoic anhydride under microwave irradiation reveals that an equimolar mixture of these materials quickly fuses with a slight amount of dimethylformamide to give good yields of the product **3** (Table 2).

Path B begins with nucleophilic attack of the primary amine on C-4 of isatoic anhydride resulting in 2-aminobenzanilides **2**, due to concomitant liberation of CO_2. This step is followed by cyclocondensation of formic acid with

Table 1. Physical data of the products **3a–f**

Product	R	Yield[a] (%)	Mp (°C)	Lit. mp (°C)
3a	Ph	77	139–140	138–139[17]
3b	$PhCH_2$	80	118–119	117–118[17]
3c	3,4-$Me_2C_6H_3$	74	134–135	135[18]
3d	4-MeC_6H_4	78	146–147	148–149[19]
3e	4-$MeOC_6H_4$	69	189–190	189–191[20]
3f	4-ClC_6H_4	75	179–180	180–181[21]

[a] Yields of separated products, based on isatoic anhydride.



Scheme 1.

2-aminobenzanilide **2** to afford the product **3**. The self-condensation of isatoic anhydride is a drawback encountered in this reaction, hence an excess of the amine is usually required to supersede it.[22] When isatoic anhydride was mixed with 1.25 equivalents of a primary amine, in dry media, and then irradiated for 6 min the 2-aminobenzanilides **2** were obtained in yields similar to those obtained through the reported conventional method[22] (Table 3).

Table 2. Yields of formanilides **1** and their reaction with isatoic anhydride

	Results of reaction of R-NH$_2$ + HCOOH			Results of reaction of 1 + isatoic anhydride		
R	Product	Yield (%)[a]	Time	Product	Yield (%)[b]	Time
4-MeOC$_6$H$_4$	**1e**	60	4 min	**3e**	62	6 min
4-ClC$_6$H$_4$	**1f**	74	4 min	**3f**	71	6 min

[a] Yields based on amines.

[b] Yields based on isatoic anhydride.

Table 3. Physical data of 2-aminobenzanilides **2** and their reaction with formic acid

	Results of reaction of RNH_2 + isatoic anhydride					Results of reaction of **2** + HCOOH		
R	Product	Yield (%)[a]	Time	Mp (°C)	Lit. mp (°C)	Product	Yield (%)[b]	Time
4-MeC_6H_4	**2d**	82	6 min.	150–151	150–151[22]	**3d**	85	6 min.
4-ClC_6H_4	**2f**	70	6 min.	139–140	140–141.5[22]	**3f**	81	6 min.

[a] Yields based on isatoic anhydride.

[b] Yields based on **2**.

Microwave-assisted cyclocondensation of formic acid with 2-aminobenzanilides **2**, like the corresponding conventional heating method, takes place efficiently,[23,24] albeit in much less time and in the absence of any solvent (Table 3).

All of the products are known compounds and their melting points, IR, and ^{1}H NMR spectral data are in good agreement with those of the literature, as well as being identical with authentic samples prepared using previously reported methods.

In conclusion, we introduced here a facile method for the synthesis of 3-substituted quinazolin-4(3H)-ones from simple starting materials. The notable advantages of this methodology are mild conditions in a solvent-free system, fairly high yields, fast reaction, and safe and environmentally benign conditions.

EXPERIMENTAL

Melting points were measured on a Mettler FP5 and are uncorrected. Microwave irradiation was carried out in a 1000-W domestic microwave oven at 2450 MHz. To control the reaction, irradiations were carried out in two stages with a cooling time between them. Chemicals were obtained from Merck (Darmstadt, Germany) and were used without further purification.

General Procedure for Synthesis of 3-Substituted Quinazolin-4(3H)-ones(3a–f)

A mixture of isatoic anhydride (1.63 g, 10 mmol), formic acid (0.7 g, 15 mmol), and an appropriate primary amine (12.5 mmol in each case) was placed in a 100-mL beaker. The beaker was covered with a stemless funnel, and then irradiated in the microwave oven for 2 min with a power of 180 W. After a cooling time of about 4 min, to room temperature, the beaker was irradiated again for 6 min at 300 W. The resultant residues were crystallized from ethanol–1 M NaOH (9 : 1).

Preparation of Formanilides (1e, 1f) under Microwave Irradiation

A mixture of formic acid 0.92 g (20 mmol) and the amine (10 mmol) was placed in a 100-ml beaker. The beaker was covered with a stemless funnel, and then irradiated in the microwave oven for 4 min with a power of 180 W. The reaction mixture solidified on cooling to room temperature, and the obtained solids were recrystallized from diethyl ether–petroleum ether.

Reaction of Formanilides with Isatoic Anhydride under Microwave Irradiation

A mixture of 1.3 g (8 mmol) of isatoic anhydride, 10 mmol of formanilide (**1e** or **1f**), and a few drops of dimethylformamide contained in a 100-mL beaker was irradiated with a power of 400 W for 6 min. The resultant residue, which solidified on cooling to room temperature, was recrystallized from ethanol (95%) to give the products **3e** or **3f**.

Preparation of 2-Aminobenzanilides (2d, 2f) under Microwave Irradiation

A mixture of 1.3 g (8 mmol) of isatoic anhydride and 10 mmol of the proper amine was placed in a 100-mL beaker. The beaker was covered with a stemless funnel and irradiated in the microwave oven with a power of 300 W for 3 min. After 4 min and cooling to room temperature, the beaker was again irradiated with 300 W for 3 min. The resultant residue was recrystallized from ethanol (95%).

Reaction of 2-Aminobenzanilides with Formic Acid under Microwave Irradiation

A mixture of 10 mmol of 2-aminobenzanilide (**2d** or **2f**) and 0.92 g (20 mmol) of formic acid was placed in a 100-mL beaker. The beaker was covered with a stemless funnel, and then irradiated in the microwave oven with a power of 180 W for 3 min. After a delay time of about 4 min, when it cooled to room temperature, the beaker was again irradiated for 3 min with a power of 300 W. The resultant residue, which solidified on cooling to room temperature, was recrystallized from ethanol–NaOH 1 M (9 : 1) to give the products **3d** or **3f**.

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