A Green, Facile, and One-pot Synthesis of 2,4-(1*H*,3*H*)-Quinazolinediones under Microwave Irradiations

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Quinazoline-2,4-diones are of considerable interest due to their wide pharmacological properties. Here, we have described an environmentally friendly method for the one-pot synthesis of 2,4-(1*H*,3*H*)-quinazolinediones from the reaction of anthranilic acid derivatives with urea in H_2O media under microwave irradiations. This method is simple, safe, and fast which produces high yield of products without use of any catalyst.

2,4-(1*H*,3*H*)-Quinazolinediones are versatile intermediate in the synthesis of heterocycles with pharmacological and biological properties such as anticonvulsant,[1] anti-inflammatory,[2] and antihypertensive activity.[3] Because of their remarkable applications, considerable attention has been focused on the synthesis of some of quinazolinedione derivatives from mefenamic acid,[2] 1,4-disubstituted tetrazolium salts,[4] and isatoic anhydride;[3] also, by the Bergman cyclization[5] and solid phase approaches towards quinazolinediones.[6]

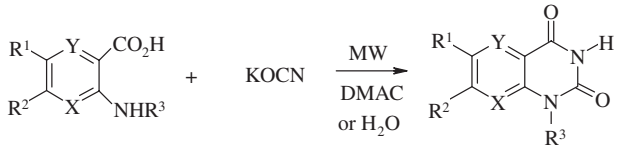
There is a great interest in the rapid synthesis of a variety of heterocyclic compounds under microwave irradiation and perceives a steadily growing interest in this research field.[7–11]

In the general method for the synthesis of 2,4-(1*H*,3*H*)-quinazolinedione,[12] toxic potassium cyanate (KOCN) is used in acetic acid solution, followed by use of concentrate solution of sodium hydroxide during overnight and addition of sulfuric acid solution for neutralization. Undoubtedly, this procedure is not an appropriate method for the synthesis of quinazolinediones with sensitive substitutions.

In this research, first, we have shown that direct condensation of anthranilic acid derivatives **1a**–**1e** with KOCN in neutral media and without use of any catalyst, provides an efficient and convenient one-pot synthesis of 2,4-(1*H*,3*H*)-quinazolindiones **2a**–**2e** in *N*,*N*-dimethylacetamide (*DMAC*) under microwave irradiations (Scheme 1).

Also, these reactions were carried out in H_2O. The results show that, although KOCN is not a good electrophile in neutral conditions, but the reactions are achieved with various substituents to produce **2a**–**2e** with good yields.

Secondly, in similar conditions, the mentioned reactions were carried out with urea instead of toxic KOCN. The results show that in all cases, the reactions proceed completely with excellent yields of products **2a**–**2f** in *DMAC* or H_2O (Table 1).



1a–1f **2a–2f**

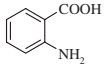
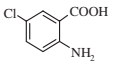
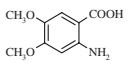
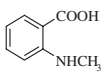
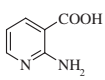
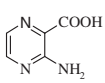
Scheme 1.

Although the compounds **1a**–**1f** are not dissolved in H_2O, it is noteworthy that for all the reactions, H_2O is a very excellent media. Also, these reactions were tested in solvent-free conditions, but no reaction was observed. Therefore, the solvent plays only as a heat transfer, so that the dehydration process is accomplished in aqueous media. Although microwave irradiations promote these reactions, however, under reflux conditions, the mentioned reactions were not completed after three hours.

In these reactions, initially nucleophilic attack of the amines on potassium cyanate or urea,[13] gives the intermediates **3a**–**3f** or **4a**–**4e** respectively (Figure 1), which upon subsequent irradiations without separation, the desired 2,4-(1*H*,3*H*)-quinazolinediones **2a**–**2f** are produced with very simple work-up.[14]

As it is observed in Table 1, when the KOCN is used, the

Table 1. Reaction of compounds **1a**–**1f** with urea or potassium cyanate under microwave irradiations

	1	Products **2**[a]					
		H_2NCONH_2			KOCN		
		Power /watt	Time /min	Yield[b] /%	Power /watt	Time /min	Yield[b] /%
a		800[c]	3[c]	96[c]	700[c]	1.5[c]	84[c]
		800[d]	3[d]	95[d]	700[d]	2[d]	75[d]
b		800[c]	2[c]	87[c]	700[c]	2[c]	85[c]
		800[d]	4.5[d]	90[d]	700[d]	0.5[d]	88[d]
c		800[c]	2[c]	90[c]	700[c]	3[c]	85[c]
		800[d]	3[d]	86[d]	700[d]	1[d]	8[d]
d		800[c]	3[c]	95[c]	700[c]	1.5[c]	88[c]
		800[d]	6[d]	85[d]	700[d]	1.5[d]	52[d]
e		800[c]	3[c]	83[c]	700[c]	1.5[c]	80[c]
		800[d]	4.5[d]	95[d]	700[d]	0.5[d]	95[d]
f		800[c]	3[c]	88[c]	700[c]	1.5[c]	0[c]
		800[d]	3[d]	87[d]	700[d]	1.5[d]	0[d]

[a]In all cases, the products were identified and characterized by comparison of their physical and spectral data with those of authentic samples. [b]Isolated yields. [c]In DMAC. [d]In H_2O.

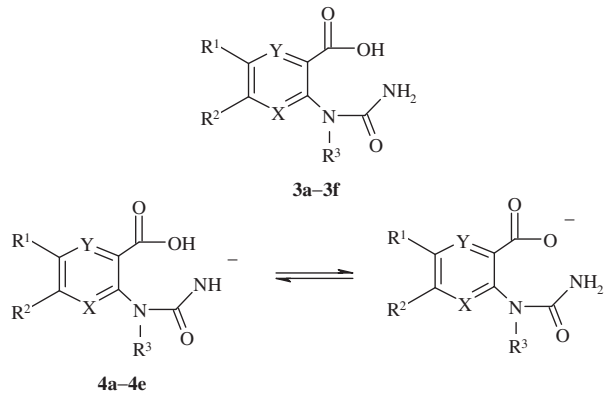


Figure 1.

yield of **2c** in H_2O is very low; also, **2f** is not produced in *DMAC* or H_2O at all. The reasons are as follows:

First of all, in the case of **1c**, high nucleophilicity of amine, owing to the presence of a methoxy group in para-position, increases the reaction rate in the first step, but substitution of another methoxy group in para-position to the carboxylic acid, decreases the cyclization reaction rate of **4c**; therefore, this reaction is carried out in *DMAC* (bp 166 °C), but because of the lower boiling point of H_2O in comparison with *DMAC*, the heat transfer to the reaction mixture, is not accomplished completely and before completion of the reaction, the water is evaporated. Similarly, the solvent plays as a heat transfer in the reaction of **1d** with KOCN; however, in H_2O, owing to the steric hindrance of nucleophile, the reaction is not fulfilled completely but is accomplished in *DMAC* entirely.

Secondly, substitution of two nitrogen atoms in the benzene ring of **1f**, makes it a very week nucleophile, which can not attack KOCN in neutral media. Therefore, the intermediate **4f** is not formed and **2f** is not obtained.

In conclusion, the present procedure demonstrates a simple and fast method for the synthesis of 2,4-(1*H*,3*H*)-quinazolinediones in neutral media without use of any catalyst, which can be used for a variety of substituents. Also, especially when urea is used in H_2O, this method is clean and safe, which provides excellent yields of the desired products of high purity with simple work-up and shows a green and environmentally friendly reaction.

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References and Notes

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14 Microwave irradiations were carried out in a Butane oven Model MB310. Substances were commercially prepared (Merck and Fluka) and used.
Caution! For more safety, especially when *DMAC* are used as solvent, all experiments should be performed in an efficient hood in order to avoid the contact of vapors.
General procedure: A mixture of 5 mmol anthranilic acids **1a–1f**, 0.3 g (5 mmol) of urea or 0.4 g (5 mmol) of potassium cyanate, and 0.5 mL of *DMAC* or 1 mL distilled water (hot water in the case of **1d**) contained in a 30 mL tall beaker (equipped with a simple funnel on it) was placed in the microwave oven and irradiated with power and time as indicated in Table 1. The reaction mixture was cold to room temperature, then 5 mL of H_2O was added and mixed with the contents and decanted (three times). The products collected and dried first in air then in oven (100 °C). The raw products were recrystallized from ethanol, or ethanol/acetic acid.

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