SHORT PAPER

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An expeditious and solvent-free route to the synthesis of 2-substituted quinazolin-4(3*H*)-ones under microwave conditions†

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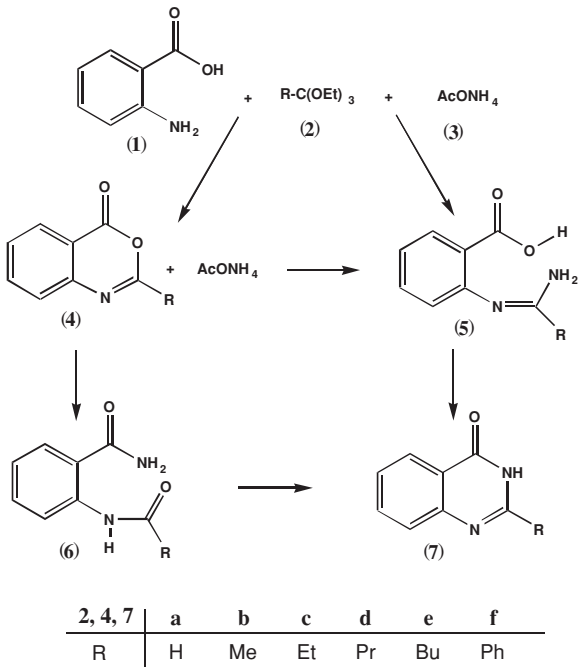
Ammonium acetate condenses with benzoxazinones (**4b–e**) or a mixture of anthranilic acid and orthoesters in the absence of solvent to produce the title compounds in a few minutes.

Keywords: quinazolin-4(3*H*)-ones, microwave, anthranilic acid, 3,1-benzoxazin-4-ones

Those quinazolin-4(3*H*)-ones which bear no substituent at the 3-position are well known as a class of biologically active compounds.[1] They also serve as precursors to the synthesis of elaborated quinazolines.[2] So, many methods have been developed for their synthesis in which, more often, anthranilic acid or its derivatives are used in reaction with C-2 and N-3 supplying reactants.[3] In continuation of our previous work on microwave-assisted synthesis of quinazolin-4(3*H*)-ones,[4] we now report a one-pot cyclocondensation of anthranilic acid with orthoester and ammonium acetate under microwave irradiation. To our knowledge there has been no report of the use of ammonium acetate as a separate synthon for N-3 in a solventless three-component synthesis of quinazolin-4(3*H*)-ones.

Thus, a mixture of the starting materials was irradiated under microwave and thereby fairly high yields of the products (**7a–f**) were obtained in a few minutes.

The mechanism of the reaction could be rationalised as a direct formation of the intermediate amidine (**5**), which would then cyclise via amidation to afford the products (**7a–f**). An alternative proposal could be the formation of 2-substituted-3,1-benzoxazin-4-ones (**4**) from condensation of anthranilic acid with orthoesters,[5] which as transients could undergo subsequent nucleophilic attack of ammonia at the 2-position to provide the inermediate amidines (**5**).[6] It is worth considering the intermediacy of 2-amidobenzamides (**6**), since they may be produced by the attack of ammonia at the 4-position of the benzoxazinones, and could cyclodehydrate under thermal conditions.[7] However, we observed that a mixture of benzoxazinones **4b–e**[8] and ammonium acetate fused with a drop of acetic acid under microwave irradiation affords the expected quinazolin-4(3*H*)-ones (**7b–e**) in fairly high yields (see Table 1). But **4f** under similar conditions gave only **6f**, and this would seem to rule out the formation of benzoxazinones (**4**) in the three-component reaction.



Scheme 1

Most quinazolin-4(3*H*)-ones have been synthesised by cyclocondensation of anthranilamides with a variety of reactants,[13] or through the intermediacy of *o*-amidobenzamides.[14] Earlier methods related to this route made use of NH_3 solutions in reaction with methyl anthranilate and dimethylformamide dimethylacetal,[15] with amidine derivative of methyl anthranilate,[16] or in a relatively prolonged reaction with benzoxazinones.[6,7] However, use of ammonium acetate (**3**) in the methodology

Table 1 Yields and conditions of quinazolinone formation

Compd	*R*	Yield (%)[a] of reaction **1**+**2**+**3** Microwave	Reflux	Yield[a] of reaction **4**+**3** Microwave		M.p./°C	Lit. m.p./°C
	(time)	(time)	(time)				
7a	H	93 (6 min.)	89 (3.5 h)	—	—	216–218	216–217[c]
7b	Me	90 (6 min.)	87 (5 h)	82 %	(5 min.)	236–238	236–238[d]
7c	Et	92 (6 min.)	87 (5 h)	83 %	(5 min.)	224–226	226–227[e]
7d	n-Pr	88 (6 min.)	85 (5 h)	79 %	(5 min.)	194–196	190–192[e]
7e	n-Bu	86 (6 min.)	83 (5 h)	77 %	(5 min.)	157–159	158–159[f]
7f	Ph	89 (6 min.)	84 (5 h)	—	—	237–240	239–240[c]

[a]Yields of pure isolated products based on anthranilic acid or benzoxazinone. [b]In absolute ethanol. [c]Ref. 10. [d]Ref. 11. [e]Ref. 12. [f]Ref. 9.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

presented here not only leads to fairly high yields of products and short reaction times, but also it has replaced the tedious preparation of anhydrous NH_3 solutions. Also, employing the conventional refluxing conditions, we have performed the reaction using **3** in ethanolic solution. From Table 1, a comparison with the results of performing the tricomponent reaction in refluxing absolute ethanol with those obtained under solventless microwave conditions, indicates a preference for the latter method.

All of the products are known 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 introduce here a facile and efficient synthesis of the title compounds under environment-friendly solventless conditions. The reactions are clean and no by-products were detected.

Experimental

Melting points were measured with a Mettler FP5 instrument. Microwave irradiations were carried out in a domestic oven at 2450 MHz. Chemicals were obtained from Fluka and were used without further purification. In order to control the reaction, irradiations were carried out in two stages separated by a cooling interval.

*General procedure under microwave irradiation***:** A mixture of anthranilic acid (1.37 g, 10 mmole), orthoester (**2a–f,** 13 mmole) and ammonium acetate (1 g, 13 mmole) was placed in a tall beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for 2 min with a power of 210W. After a cooling time of about 5 min the beaker and contents were irradiated again at 210 W for 4 min. The resultant residues were triturated with water, filtered off, and recrystalised from aqueous ethanol.

*General procedure under classical heating***:** A stirred mixture of anthranilic acid (1.37 g, 10 mmole), orthoester (**2a–f,** 16 mmole) and ammonium acetate (1 g, 13 mmole) in absolute ethanol (4 ml) was refluxed gently and the reaction progress was followed by TLC (Et_2O: EtOAc, 3 : 1). After the time required for the anthranilic acid to diminish to a trace (see Table) the reaction mixture was cooled to room temperature and the white product thus obtained was filtered off and recrystallised from aqueous ethanol.

Alternative procedure for preparation of **7b–e** *under microwave heating:* To an intimate mixture of benzoxazinone (**4b–e**, 5 mmole) and ammonium acetate (0.5 g, 6.5 mmole) in a tall beaker was added one drop of glacial acetic acid. The beaker was covered with a stemless funnel and irradiated for 5 min. at 210 W. The resultant residues were worked up as mentioned above.

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