MICROWAVE IRRADIATION PROMOTED REACTIONS OF BENZOXAZIN-4-ONES WITH PRIMARY AMINES. PREPARATION OF 4(3H)-QUINAZOLINONES

Khajavi, Mohammad Sadegh ; Sadat Hosseini, Seyed Saheb and Montazari, Nasser*
Department of Chemistry, Faculty of Science, Shahid Beheshti University,
Tehran, I.R. Iran

ABSTRACT: *An efficient synthesis of 3-substituted or 2,3-disubstituted 4(3H)-quinazolinones from benzoxazin-4-ones and primary amines under microwave irradiation in unsealed vessels is described.*

KEY WORDS: *Microwave irradiation, Quinazolinones, Benzoxazin-4-ones.*

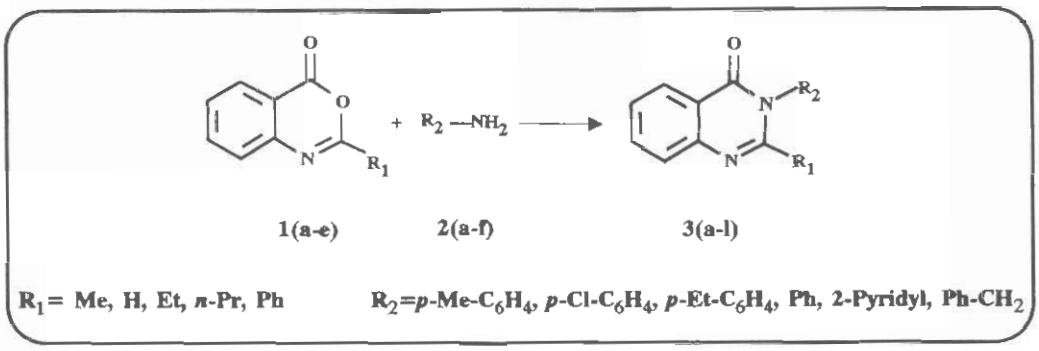
Microwave irradiation promoted organic condensation has attracted intense interest as a synthetically useful technique for the preparation of a variety of heterocyclic compounds [1-6]. We have recently described a new and high efficient method for the synthesis of 2-substituted 4H-3,1-benzoxazin-4-ones by the condensation of readily available anthranilic acid and orthoesters under classical heating or microwave irradiation [7]. In this report, we wish to demonstrate the utility of microwave irradiation by the synthesis of a number of variously substituted 4(3H)-quinazolinones from 4H-3,1-benzoxazin-4-ones and primary amines.

4(3H)-Quinazolinones are reported to exhibit a wide spectrum of biological activities including anticonvulsant activity [8], analgesic [9], anti-inflammatory [10], anti-pyretic and diuretic property [11]. Quinazolinones are normally prepared by treatment of O-acyl anthranil with primary amines at temperatures above 200°C [12]. Other synthetic methods includes treatment of phosphoranes with NaH/CH_3CN [13], dimerization of substituted anthranilic acid under Vilsmeier condition [14] and pyrolysis of Schiff bases derived from 3-amino-1,2,3-triazin-one in paraffin oil at 300°C [15].

We have found that when a mixture of 2-methyl-4H-3,1-benzoxazin-4-one (**1a**) and *p*-tolylamine (**2a**) in N,N-dimethylacetamide (DMAC) was irradiated for 7 min in microwave oven, 2-methyl-3-*p*-tolyl-4(3H)-quinazolinone (**3a**) was isolated in 92% yield (Scheme 1).

In this reaction DMAC, with a high dielectric constant, proved to be the most effective solvent, giving optimum yields of product when compared to dimethylformamide, chlorobenzene and dioxane [16-18]. DMAC provides a clean and faster reaction. The reaction was performed in a tall beaker covered with a stemless funnel. The irradiation was carried out in

* *To whom correspondence should be addressed.*
1021-9986/99/1/30 3/$/2.30



Scheme 1

two stages with a cooling period between each stage. To optimize the yields, a different power was used for each stage of irradiation (Table 1).

In all cases the products were identified by their spectroscopic properties and comparison with authentic samples [19-27].

EXPERIMENTAL

^{1}H NMR spectra were obtained on a Bruker AC 80 or JEOL-EX-90 instrument. IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrophotometer. Microwave irradiations were carried out in a National oven, model 5250, at 2450 MHz. Melting points are uncorrected and were determined in open capillary tubes using Thomas-Hoover apparatus.

For safety reasons all the experiments with microwave ovens should be performed in an efficient hood in order to avoid contact with vapours. If a tall beaker covered with a watch glass or a small stemless funnel is used and the microwave irradiation period is interrupted with a 5 min cooling time; there is a little vaporization and very high conversion can be observed.

Preparation of substituted 4(3H)-quinazolinones under microwave irradition:

The general procedure is illustrated for preparation of 2-methyl-3-*p*-tolyl 4(3H)-quinazolinone (**3a**). A mixture of 2-methyl-4H-3,1-benzoxazin-4-

Table 1: Reaction of 4H-3,1-benzoxazin-4-ones with primary amines

Entry	Product	R_1	R_2	Irradiation conditions[a]				Yield	mp	lit.mp
				(1)P/W	t/min	(2)P/W	t/min	(%)[b]	(°C)	(°C)
1	3a	Me	*p*-Me-C_6H_4	210	3	385	4	92	151-152	151-152[26]
2	3b	Me	*p*-Cl-C_6H_4	210	3	385	4	83	156-157	157-158[19]
3	3c	Me	*p*-Et-C_6H_4	385	4	490	2	88	148-150	150-152[27]
4	3d	Me	Ph	210	3	385	3	90	146-147	147-148[26]
5	3e	H	*p*-Me-C_6H_4	385	5	490	3	95	143-144	143-145[20]
6	3f	H	$PhCH_2$	210	3	385	5	90	115-116	115-116[21]
7	3g	Me	2-Pyridyl	210	2	385	4	88	162-163	164-165[22]
8	3h	Et	*p*-Me-C_6H_4	385	6	490	2	94	160-162	162-163[23]
9	3i	*n*-Pr	*p*-Me-C_6H_4	210	3	385	4	92	145-146	145[23]
10	3j	*n*-Pr	Ph	210	3	385	3	95	121-122	122-123[23]
11	3k	Ph	Ph	385	3	490	2	82	158-159	158-158.5[24]
12	3l	Ph	*p*-Me-C_6H_4	385	5	490	2	90	180-181	180-181[25]

a : To control the reaction, the irradiation was carried out in two stages, with a cooling time between each stage.

b : Yield of pure isolated product based on benzoxazin-one.

one (3.22 g, 20 mmol) and *p*-tolylamine (2.14 g, 20 mmol) in 5 mL of N,N-dimethylacetamide contained in a tall beaker was placed in the microwave oven and the beaker was covered with a stemless funnel and irradiated for 3 min at 210 Watts, after 5 min for litting it cools slowly to room temperature, it was irradiated again at 385 Watts for 4 min. Then the reaction mixture was allowed to cool to room temperature and the precipitate thus obtained was filtered off and recrystallized from ethanol and ether to give pure product in 92% yield, mp 151-152°C (lit [26], 151-152°C).

IR(KBr): 3025, 1684, 1602, 1565, 1504 cm^{-1}.

^1H NMR($CDCl_3$): 2.32(S, 3H, CH_3), 2.42(S, 3H, CH_3), 7.14-8.28(m, 8H, Ar-H).

Received, 23rd February 1998; Accepted, 4th January 1999

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