MICROWAVE IRRADIATION PROMOTED THE NIEMENTOWSKI REACTION. PREPARATION OF SUBSTITUTED QUINAZOLINONES AND QUINOLINES☆

Khajavi, Mohammad Sadegh; Afshani, Parichehr and Rad Moghadam, Kourosh*
Department of Chemistry, Faculty of Science, Shahid Beheshti University,
Tehran, I.R. Iran

ABSTRACT: *The first highly accelerated Niementowski reaction of anthranilic acid with some amides or ketones under microwave irradiation leading to quinazolinones and quinoline derivatives is described. These reactions represent some examples of efficient microwave irradiation promoted organic condensation in which the reactions can be carried out in open vessels and provides products of high purity with simple work up.*

KEY WORDS: *Microwave irradiation, Anthranilic acid, Niementowski reaction, Quinolines, Quinazolinones.*

The rapid synthesis of a variety of organic compounds under microwave irradiation has been widely demonstrated [1-4]. In recent years, the application of this technique as an efficient and controllable thermal source has been actively studied for the heterocyclic synthesis [5-8]. We have recently described an efficient and rapid synthesis of a variety of heterocyclic compounds under microwave irradiation in an unmodified commercial microwave oven using unsealed vessels [9]. We present here some preliminary results concerning the utility of microwave irradiation by the synthesis of a number of variously substituted quinazolinones and quinoline derivatives from anthranilic acid and different "two-atom linchpin" reagents.

RESULTS AND DISCUSSION

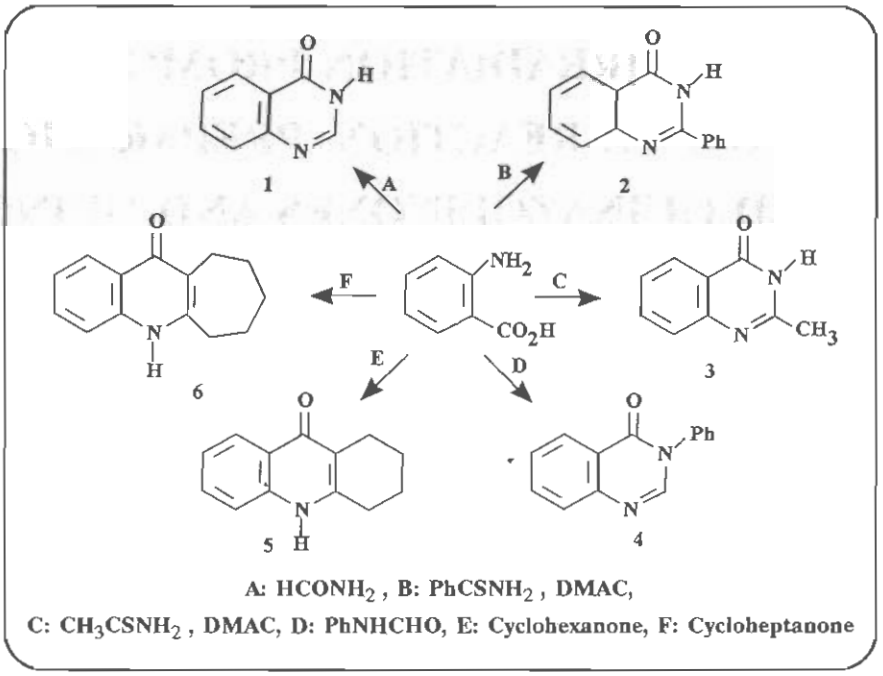
The synthesis of many compounds containing these heterocycles has attracted much attention because of their potential and wide range of pharmacological activities [10] and in particular medicinal important quinoline, quinazoline and acridone alkaloides [11].

In general, the most common method for the synthesis of substituted 4-keto-3,4-dihydroquinazolines involves the Niementowski reaction [12] (condensa-

☆ *Dedicated to Professor Abbas Shafiee on the occasion of his 60th birthday.*

* *To whom correspondence should be addressed.*

1021-9986/98/1/29 4/$/2.40



Scheme

tion of anthranilic acid and amides) and of acridones, the Niementowski modification of the Freidländer synthesis [13] by heating a mixture of anthranilic acid and a ketone. In practice this approach is restricted to carry out conveniently because the temperatures required for the ring closures can not be attained or maintained without decarboxylation of anthranilic acid [13,14].

We have found that the condensation of anthranilic acid with formamide results in the rapid formation of 4-quinazolinone **1** in high yield when subjected to microwave irradiation (Scheme). Thus, treatment of anthranilic acid with excess of formamide in a beaker covered by a stemless funnel and irradiation for a few minutes after usual work up gives the desired 4-quinazolinone **1** in nearly quantitative yield. A conventional method of preparation of **1**, takes 4 hours with a yield of 90% is reported [15].

While benzamides do not undergo the Niementowski reaction, thioamides does react. The reaction of thiobenzamide or thioacetamide with anthranilic acid in *N,N*- dimethylacetamide (DMAC) [16], on short microwave irradiation, efficiently produced 2-phenyl-4(3H)quinazolinone **2** and 2-methyl-4(3H)-quinazolinone **3** respectively (Scheme). The conventionally thermolysed reactions [15] for the preparation of **2** and **3** required significantly longer reaction times (2 hours) and lower yields (50%).

Similarly, the microwave preparation of 3-phenyl-4(3H)quinazolinone **4** from formanilide and anthranilic acid proceeded cleanly, with a reaction time of 10 minutes in 88% yield. The corresponding conventional preparation [17] of **4** after 10 hours resulted the desired product is only 40% yield.

Furthermore, condensation of anthranilic acid and cyclohexanone under microwave irradiation led to the evolution of water and the formation of 1,2,3,4-tetrahydro-9(10H)acridinone **5** in high yield [13]. When cycloheptanone was used in the same manner the expected acridone **6** was isolated with no significant change in reaction conditions [18].

Furthermore, in order to find the best reaction conditions, the reaction mixtures were irradiated for variable times, microwave power and in different molar ratios of the reactants. The results are summarized in Table.

In summary, we have developed a convenient, efficient and rapid procedure for the synthesis of quinazolinones and quinoline derivatives using household unmodified microwave oven. The remarkable fea-

Table : Reaction of anthranilic acid with reagents A-F(Scheme).

Product	Irradiation condition[a]				Solvent	A-F(equiv)	yield[b]
	(1)P/W	t/min	(2)P/W	t/min			
1	210	2	385	2	—	6	98
2	210	2	—	—	DMAC[20]	1	86
3	210	3	385	3	DMAC[20]	1.1	81
4	210	6	385	4	—	2	88
5	210	1	385	3	—	3	92
6	210	1	385	4	—	2	83

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

b: Yield of pure, isolated product base on anthranilic acid

tures of this new process are the operational simplicity and simple work up of the reaction mixtures which provides products of high purity. Work is continuing in this area to extend these reactions to other heterocyclic systems.

EXPERIMENTAL

All products are known compounds and their physical data, infrared and NMR spectra were essencially identical with those of authentic samples. Microwave irradiation were carried out in a National oven, model 5250 at 2450 MHz.

General procedure

A mixture of anthranilic acid (2.74 g, 20 mmol) and (i) formamide (5.4 g, 120 mmol), (ii) thiobenzamide (2.74 g, 20 mmol) and DMAC (5 mL), (iii) thioacetamide (1.65 g, 22 mmol) and DMAC (5 mL), (iv) formanilide (4.84 g, 40 mmol), (v) cyclohexanone (5.9 g, 60 mmol), (vi) cycloheptanone (4.48 g, 40 mmol), contained in a tall beaker was placed in the microwave oven, the beaker was covered with a stemless funnel and irradiated with power and time as indicated in Table. The reaction mixture was allowed to cool to room temperature and the resultant residue recrystallized from ethanol to afford the pure products 1-6.

Received, 12th January 1997 ; Accepted, 3rd March 1997

REFERENCES

[1] Gedye, R. N., Smith, F. E., Westaway, K. C., Ali, H., Baldisera, L., Laberge, L. and Rousel, J., *Tetrahedron Lett.*, **27,** 279(1986).

[2] Gedye, R. N., Smith, F. E. and Westaway, K. C., *Can. J. Chem.*, **66,** 17(1988).

[3] Giguere, R. J., Bray, T. L., Duncan, S. M. and Majetich, G., *Tetrahedron Lett.*, **27,** 4945(1986).

[4] a) Caddick, S., *Tetrahedron,* **51,** 10403(1995).
b) Mingos, D. M. and Baghurst, D. R., *Chem. Soc. Rev.*, **20,** 1(1991).

[5] Bose, A. K., Banik, B. K. and Manhas, S. M., *Tetrahedron Lett.*, **36,** 213(1995) and references cited therein.

[6] Alajarin, R., Jordan, P., Vaquero, J. J. and Alvarez-Builla, *Synthesis,* 389(1995) and references cited therein.

[7] Jones, G. B. and Chapman, B. J., *J. Org. Chem.*, **58,** 5558(1993).

[8] Oussaid, B., Moeini, L., Martin, B., Villemin, D. and Garrigues, B., *Synth. Commun.*, **25,** 1451 (1995).

[9] a) Khajavi, M. S., Hajihadi, M. and Naderi, R., *J. Chem. Res.(S),* 92(1996).
b) Khajavi, M. S., Hajihadi, M. and Nikpour, F., *J. Chem. Res.(S),* 94(1996).
c) Khajavi, M. S., Nikpour, F. and Hajihadi, M., *J. Chem. Res.(S),* 96(1996).

[10] a) Tzantrizos, Y. S., XU, X.-J., Sauriol, F. and

Hynes, R. C., *Can. J. Chem.*, **71,** 1362(1993).
b) Rasmussen, L. E. L., Lee, T. D., Daves, Jr., G. D. and Schmidt, M. J., *J. Chem. Ecol.*, **19,** 2115 (1993).
c) Groundwater, P. W. and Solomons, K. R. H., *J. Chem. Soc., Perkin Trans., 1,* 173(1994).
d) Palazzo, S. and Giannola, L. I., *J. Heterocycl. Chem.*, **10,** 675(1973).
e) Parmar, S. S., Kishor, K. and Seth, P. K. and Arora, R. C., *J. Med. Chem.*, **12,** 138(1969).

[11] Michael, *J. P. Nat. Prod. Rep.*, **12,** 465(1995).

[12] Hassner, A. and Stumer, C., Organic Syntheses Based on Name Reactions and Unnamed Reactions; Baldwin, J. E. and Magnus, P. D., *Tetrahedron Organic Chemistry Series* Vol. **11,** Pergamon press, Oxford, p. 275(1994).

[13] Tiedtke have reported that the reaction of anthranilic acid with cyclohexanone under thermal activation afforded acridinone 5 in 40% yield: Tiedtke, H., *Chem. Ber.*, **42,** 621(1909).

[14] Meyer, J. F. and Wagner, E. C., *J. Org. Chem.*, **8,** 239(1943).

[15] Endicott, M. M., Wick, E., Mercury, M. L. and Sherrill, M. L., *J. Am. Chem. Soc.*, **68,** 1299 (1946).

[16] In these reactions, DMAC was chosen as the optimum solvent because of its excellent microwave energy-transfer [9] and faster reaction time.

[17] Koelsch, C. F., *J. Am. Chem. Soc.*, **67,** 1718 (1945).

[18] For conventional method of preparation of products 5 and 6 see refs. [13] and [19].

[19] Lee, C. M., Belg. Patent, 658 695(1965), *Chem. Abstr.*, **64,** 9693e (1966).

[20] The same reactions under thermal activation, for the same length of time produced only a small amount of the products.