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Microwave-Assisted Cyclocondensation for the Synthesis of 3-Aryl-2-thioquinazolin-4(3*H*)-ones

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An efficient synthesis of 3-aryl-2-thioquinazolin-4(3*H*)-one **1a-f** is given by the condensation of anthranilic acid and dithiocarbamate triethylammonium salts of substituted aniline in ethanol as solvent under microwave irradiation.

Key Words: Quinazoline, Microwave, Anthranilic acid, Dithiocarbamate salt.

INTRODUCTION

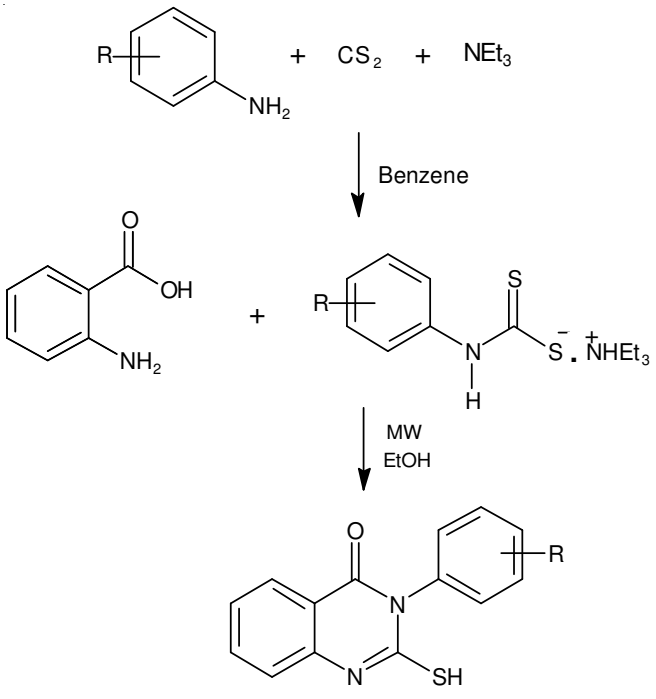
Nitrogen containing heterocycles has been paid to a large amount of attention in the literature. It is because of consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance. Of these heterocycles, quinazoline and its derivatives are reported to show characteristic biological activities[1,2], especially antihistaminic[3], antiinflammatory[4], anti HIV[5], antifungal[5,6], insecticidal[7], antibacterial[8], anticonvulsant[9], antihypertensive[10], antimicrobial[11,12], antitubercular[13], antitumor[14]. In this paper, we report a new method for the synthesis of 3-aryl 2-thio-derivatives of quinazolinone.

Nowadays microwave heating is a non-conventional energy source for activation of organic synthesis. It has attracted considerable interest due to the generally short reaction times, enhanced reaction rates, easier work-up and the resulting products with high purity and yields[15-17]. The high efficiency of microwave irradiation in promoting organic reaction and the success of its application in heterocyclic synthesis[18] triggered us to apply it to heterocyclization.

Microwave-assisted syntheses have been investigated extensively using organic solvents in open vessels. High boiling microwave-absorbing solvents have shown a great promise for this purpose. But the use of solvents has limited the advantages in relation to product isolation.

Herein the microwave irradiation promoted cyclocondensation of anthranilic acid and thiocarbamate salt of variously substituted anilines is the convenient practicing way for forming a series of 3-aryl 2-thioquinazolinone (**Scheme-I**).

Moreover, we performed the synthesis of **1a-f** under microwave irradiation with solvent, microwave irradiation without solvent and conventional heating condition. The reactions were efficiently promoted by microwave irradiation and the reaction time was strikingly shortened to 20-30 min for microwave irradiation with solvent from 5-6 h required under traditional heating condition and the yields were increased from 70-75 to 80-85 %. But when the reaction is



1 a-f

R = *p*-Cl, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *p*-Br

Scheme-I

carried out in microwave irradiation without solvent, the reaction time was again shortened to 2-3 but the yields were considerably decreased to 44-55 %. Therefore, microwave irradiation exhibited several advantages over the conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield owing to a specific non-thermal microwave effect.

EXPERIMENTAL

Melting points were uncorrected and were measured with melting point apparatus DBK programmable melting point apparatus. IR spectra (KBr) were obtained on a Thermo Nicolet Nexus 670 FT-IR spectrometer. ^{1}H NMR spectra were determined on Avance-300 spectrometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal reference. Microwave irradiation was carried out with commercial Catalytic System Microwave Synthesizer (750 W). Dithiocarbamate triethylammonium salts were synthesized by reported method[19]. All reagents were commercially available.

General procedures for the preparation of 3-aryl-2-thioquinazolin-4-(3*H*)-one (1a-f): The synthesis of 3-(4-chlorophenyl)-2-thioquinazolin-4-(3*H*)-one (**1a**) is described as a representative example.

Method 1

Conventional heating: The dithiocarbamate triethylammonium salt of *p*-chloroaniline (6.37 g, 0.05 mol) and anthranilic acid (7.2 g, 0.05 mol) in 15 mL ethanol were refluxed on water bath for 6 h. After cooling the crude product was filtered and washed twice with a little water. The product was dissolved in 10 % alcoholic NaOH and reprecipitated by dilute hydrochloric acid. The resultant residue was crystallized from ethanol.

Method 2

Microwave irradiation with ethanol as solvent: The dithiocarbamate triethylammonium salt of *p*-chloroaniline (6.37 g, 0.05 mol) and anthranilic acid (7.2 g, 0.05 mol) in 10 mL ethanol were taken in a long-necked flask. The flask was connected to condenser fitted in microwave synthesizer and then irradiated at 245-280 watt, under stirring for the time indicated in Table-1. For each 20-30 min irradiation the process was stopped after every 30 s to avoid overheating (monitored by TLC). After cooling the crude product was filtered and washed twice with a little water. The product was dissolved in 10 % alcoholic NaOH and reprecipitated by dilute hydrochloric acid. The resultant residue was crystallized from ethanol.

Spectral characterization of 1a: IR (KBr, ν_{max}, cm^{-1}): 3330-3125 (-SH), 1665 (>C=O), 1610 (C=N). ^{1}H NMR (DMSO-d_6): δ 7.2-8.1 (8H, m, Ar-H), 10.6 (1H, s, -SH) ppm. MS : m/s, 288 (M^+), 287 (100 %), 255, 252, 145, 119, 111, 91, 75.

Method 3

Microwave irradiation without solvent: The same method was applied which explained in method 2, but it was without solvent.

RESULTS AND DISCUSSION

Compared with method **1** and **3**, method **2** has a greater virtue. It is most suitable for industrial manufacture which consumes the least time to finish the synthesis of 3-aryl-2-thioquinazolin-4-(3*H*)-one. The microwave irradiation synthesis uses not only for least time, but it also has the greater yields. From the Table-1, we can clearly know that the microwave irradiation is a simple way to synthesize this nucleus.

It was also observed that during operation of microwave we got better yields in presence of solvent than without solvent. But the time required to complete the reaction with solvent is more than the time required to do so without solvent.

In this paper, we report microwave assisted syntheses of 3-aryl-2-thioquinazolin-4-(3*H*)-one by condensation of anthranilic acid and dithiocarbamate salt of substituted anilines in solvent and solvent free condition and compare it with the conventional method. As a result, the microwave irradiation with solvent is the simple way to synthesize 3-aryl-2-thioquinazolin-4-(3*H*)-one.

TABLE-1
COMPARE OF THREE WAY OF SYNTHESIS OF 3-ARYL-2-THIOQUINAZOLIN-4(3*H*)-ONE

Compound	R	m.p. ºC (reported)	Conventional method yield (%)	Microwave irradiation method					
				With solvent			Without solvent		
				Watt	Time (min)	Yield (%)	Watt	Time (min)	Yield (%)
1a	*p*-Cl	307(317)[20]	76	280	20	86	350	6	57
1b	-H	304(302)[19]	75	280	30	82	350	2	52
1c	*p*-CH_3	302(298)[19]	71	280	25	84	350	5	49
1d	*m*-CH_3	294	74	280	30	79	350	6	48
1e	*p*-OCH_3	280(274)[19]	70	245	20	85	350	5	55
1f	*p*-Br	315(320)[19]	68	245	30	82	700	6	44

TABLE-2
SPECTRAL CHARACTERIZATION DATA OF COMPOUNDS **1b-f**

Comp.	R	IR (KBr, ν_{max}, cm^{-1})	H^1 NMR ($CDCl_3$/DMSO-d_6) δ (ppm)
1b	-H	3330-3100 (-SH), 1670 (>C=O), 1610 (C=N)	7.1-8.3 (9H, m, Ar-H), 10.6 (1H, s, -SH)
1c	*p*-CH_3	3325-3130 (-SH), 1690 (>C=O), 1625 (C=N)	2.4 (3H, s, -CH_3), 7.1-8.1 (8H, m, Ar-H), 10.6 (1H, s, -SH)
1d	*m*-CH_3	3325-3130 (-SH), 1690 (cyclic amido C=O), 1625 (C=N)	2.3 (3H, s, Ar-CH_3), 6.8-7.9 (8H, m, Ar-H), 11.4 (1H, s, -SH)
1e	*p*-OCH_3	3330-3100 (-SH), 1676 (cyclic amido C=O), 1620 (C=N)	3.4 (3H, s, Ar-OCH_3), 7.0-8.0 (8H, m, Ar-H), 13.0 (1H, s, -SH)
1f	*p*-Br	3330-3110 (-SH), 1672 (>C=O), 1610 (C=N)	7.0-8.1 (8H, m, Ar-H), 10.4(1H, s, -SH)

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REFERENCES

1. Y. A. Ammar, A.M.S. El-Sharief, M.A. Zahran, A.H. Ali and M.S.A. El-Gaby, *Molecules*, **6**, 267 (2001).
2. P.M.S. Bedi, V. Kumar and M.P. Mahajan, *Bioorg. Med. Chem. Lett*., **12**, 5211 (2004).
3. M.B. Raju, S.D. Singh, R.R.A. Raghu and K.S. Rajan, *Indian J. Pharm. Sci*., **69**, 853 (2007).
4. M.R. Yadav, S.T. Shirude, A. Parmar, R. Balaraman and R. Giridhar, *J. Het. Comp*., **42**, 1038 (2006).
5. V. Alagarsamy, R. Giridhar, M.R. Yadav, R. Revati, K. Ruckmani and E. De. Chercq, *Indian J. Pharm. Sci*., **68**, 532 (2006).
6. R.T. Vashi and S.B. Patel, *E. J. Chem*., **6**, 445 (2009).
7. T. Singh, S. Sharma, V. Kishore and K.A. Shrivastava, *Indian J. Chem*., **45B**, 2558 (2006).
8. A.K. Nanda, S. Ganguli and R. Chakraborty, *Molecules*, **12**, 2413 (2007).
9. T.T. Tita and M.J. Kornet, *J. Heterocycl. Chem*., **25**, 265 (1988).
10. V. Alagarsamy and U.S. Pathak, *Bioorg. Med. Chem*., **15**, 3457 (2007).
11. M.B. Deshmukh, S. Patil, S.S. Patil and S.D. Jadhav, *Indian J. Pharm. Sci*., **72**, 500 (2010).
12. N.B. Patel and J.C. Patel, *J. Heterocycl. Chem*., **7**, 923 (2010).
13. J. Kunes, J. Bazant, M. Pour, K. Waisser, M. Slosárek and J. Janota, *Farmaco*, **55**, 725 (2000).
14. J.D. Martin, P.M. Jeremiah, M.B. Alicia and D.S. Bradley, *Tetrahedron Lett*., **42**, 1851 (2001).
15. (a) A. Loupy, Microwave in Organic Synthesis, Wiley-VCH, Weinheim (2002); (b) B.L. Hayes, Microwave Synthesis: Chemistry at the Speed of Light, CEM Publishing, Matthews (2002); (c) P. Lidström and J.P. Tierney, Microwave-Assisted Organic Synthesis, Blackwell Scientific (2005); (d) C.O. Kappe, Microwaves in Organic and Medicinal Chemistry, Wiley-VCH, Weinheim (2005); (e) R. Martínez-Palou, Química en Microondas, CEM Publishing, Matthews (2006).
16. S. Kumar, M. Kapoor, N. Surolia and A. Surolia, *Synth. Commun*., **34**, 413 (2004).
17. F. Li, Q. Wang, Z. Ding and F. Tao, *Org. Lett*., **5**, 2169 (2003).
18. (a) R. Gedye, F. Smith, K. Westawaym, A. Humera, L. Baldisern, L. Laberge and J. Rousell, *Tetrahedron Lett*., **27**, 279(1986); (b) S.J. Tu, C.B. Miao, F. Fang, Y.J. Feng, T.J. Li, Q.Y. Zhuang, X.J. Zhang, S.L. Zhu and D.Q. Shi, *Bioorg. Med. Chem. Lett*., **14**, 1533 (2004); (c) S.J. Tu, T.J. Li, F. Shi, F. Fang, S.L. Zhu, X.Y. Wei and Z.M. Zhong, *Chem. Lett*., **34**, 732 (2005).
19. R. Lakhan, M. Srivastava, *Proc. Indian Acad. Sci. (Chem. Sci.)*, **105**, 11 (1993).