12th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-12) 1-30 November 2008
http://www.usc.es/congresos/ecsoc/12/ECSOC12.htm & http://www.mdpi.org/ecsoc-12

[E0012]

Statement of a methodology for the microwave-induced preparation of biologically important benzothiazolo [2, 3-b] quinazolines and its comparison with ultrasonic and classical heating

Anshu Dandia [a*], Sarita Khaturia[a], Anuj Kumar Jain[a] and Kapil Arya[b]

[a] *Department of Chemistry, University of Rajasthan, Jaipur-302004, India*
[b] *Indian Oil Corporation Limited, R & D Centre, Faridabad, Hayana-121007, India*
Email:aryakapil2001@yahoo.com

Abstract- Synthesis of substituted 3,3- dimethyl trihydro benzothiazolo[2,3-b]quinazoline-2*H*-ones a class of well established medicinally important compound is developed by the multicomponent condensation reaction of 2-amino-6-chloro-benzothiazole (**1**), substituted benzaldehydes (**2**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone, **3**) under different reactions conditions and energy sources, e.g. microwave irradiation, sonication and classical heating for comparison purposes. The use of a monomode oven allowed an accurate consideration of the temperature distribution in the microwave reaction vessel, which revealed a very strong and unexpected thermal heterogeneity. The reaction was facilitated by the presence of a trace of DMF, the catalytic role of which is demonstrated.
Key words-- Monomode reactor, Sonication, benzothiazolo [2,3-b] quinazolines, DMF

1. Introduction

Organic reactions accelerated under the influence of microwaves[1] have attracted considerable attention in the past decade and their application to multi-component reactions[2] can be adapted for high-speed parallel synthesis of a library of biologically active molecules. Chemists now commonly use microwave heating in order to accelerate thermal reactions or to control the kinetics of such syntheses. The weak microwave absorption of most organic chemicals was circumvented by the use of solid supports[3] which strongly absorbed hyper frequency beams but also acted as catalysts. As a consequence of their double properties, it was difficult to state the specific role of the hyperfrequency beam in such applications.[4] Moreover, the use of domestic microwave ovens was impeded by possible heterogeneity of the magnetic field, sometimes inducing insufficiently reproducibility.

On the other hand, the utilization of monomode systems led the microwave beam to be focused on the sample. However, an accurate comparison between microwave and classical heating could not be established without any temperature control.[5] For this reason, the most recent works were performed using infrared pyrometry[6] or optical fluorescence (thermometers fitted with fiber optic cables);[7] the first technique gave the surface temperature of the reaction mixture, whereas the second one allowed the estimation of local temperatures.

Thiazolo[2,3-b]quinazolines represent a medicinally and pharmaceutically important class of compounds, because of their diverse range of biological activities.[8] While conventional synthesis of biologically important benzothiazoloquinazoline ring system[9-12] have their own

merit, they are plagued by poor yields and difficult work-up due to multi-step long tedious procedure and effluent pollution. Consequently, there is need for further exploration of mild conditions, operational simplicity, cost of reagents with the increased variation of the substitutions in the components and better yields.

Our experience in microwave-assisted chemistry of heterocycles [13] encouraged us to establish an efficient synthesis of the benzothiazolo [2,3-b] quinazolines (**Scheme 1**). In all cases, besides resulting in good to excellent yields, our method offers much faster reactions compared to earlier published procedures at atmospheric pressure. Apart from that to check the better energy source and reaction conditions we have therefore undertaken all the parameters that could influence microwave-assisted syntheses into account. At the end of our work, which included a comparison with classical heating and ultrasonic irradiation[14] since, sonication as a non-conventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry.

2. Result and Discussion

In a multi-component condensation of 2-amino-6-chloro-benzothiazole (**1**), substituted benzaldehydes (**2**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone, **3**) under different conditions, exclusive formation of benzothiazolo [2,3-b] quinazolines (**4**) was observed (**Table-1**) and confirmed by spectral studies.

Table1 shows the synthesis of **4a** by various methods; to increase the efficiency, it was decided to perform this multi-component reaction in a more polar and high microwave absorbing solvents e.g. DMF. The identity of benzothiazolo[2,3-b]quinazolinone (**4a**) was established on the basis of chemical, spectral and analytical data. The ^{1}H NMR spectrum of **4a** showed two singlets at ẟ1.03 and 1.23 due to two methyl protons, two doublets at δ 1.57 and δ 2.28 for two CH_2 groups (forming AB pattern), one methine proton at ẟ4.68 and aryl protons at ẟ6.98-7.28. Further confirmation was based on the ^{13}C NMR and mass spectrum.

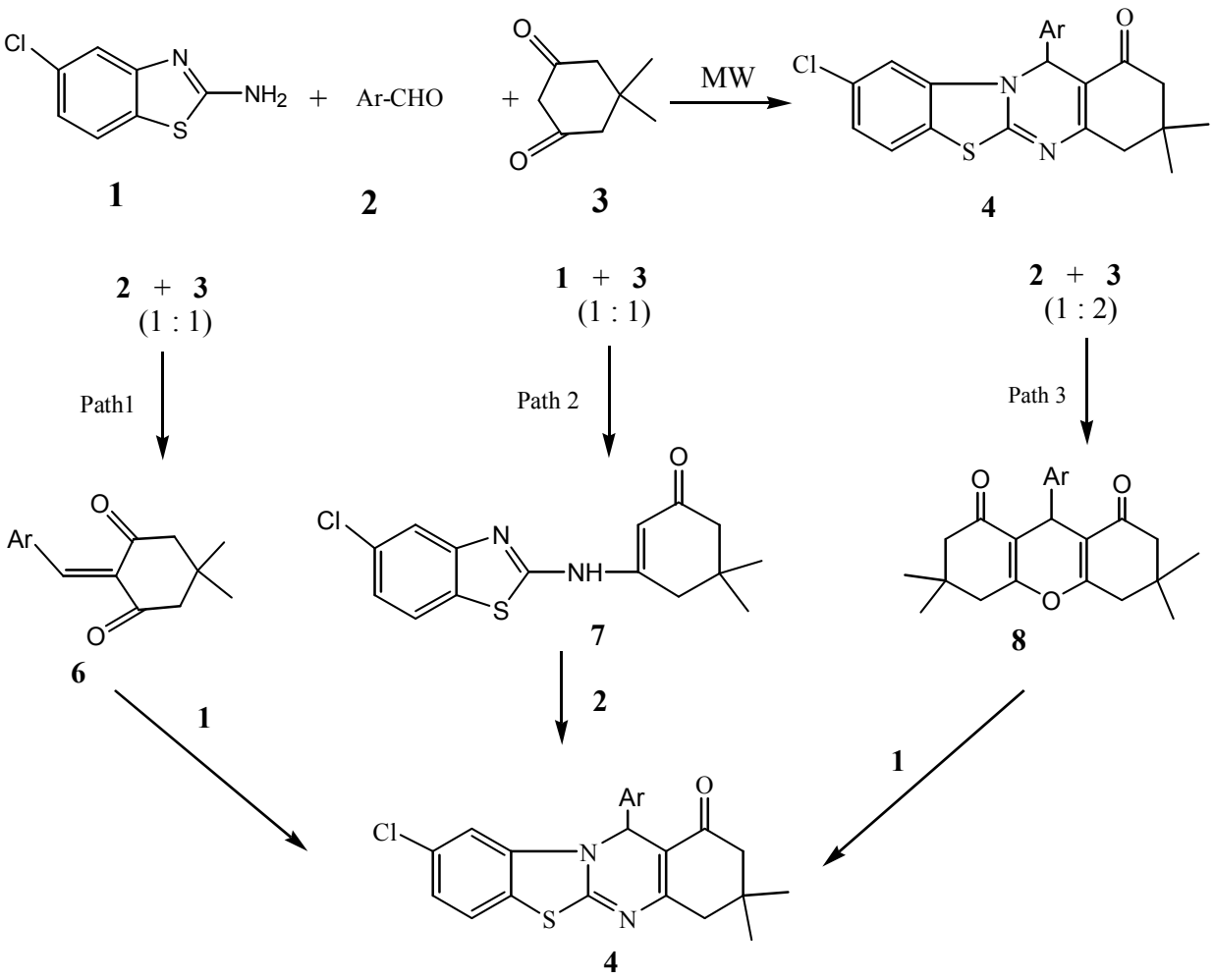
Table1. Comparative Study for the Synthesis of **4a**

Entry	Reaction medium	Reaction Temperature	Reaction time (min.) /yield(%)			
			Δ	US	MW	
					Monomode	Multimode
A.	n-butanol	100	2400/50	20/48	11/68	18/55
B.	Isopropanol	76	2640/45	25/58	18/38	15/60
C.	DMF	120	900/55	20/65	10/86	12/75

In the ^{13}C NMR, sharp signals were observed at δ 17.10 (C-(CH_3)$_2$), 27.82 (-CH_3), 29.21 (-CH_3), 45.24 (-CH_2), 47.38 (-CH_2), 50.08 (methine carbon), 116.02-127.09 (aromatic carbons),

162.09 (C=N) and 191.22 (C=O). The appearance of molecular ion peak, m/z at 429 showed the formation of benzothiazoloquinazoline (**4a**).

T



4a) Ar = 4-Cl.C_6H_4 ; **4b**) Ar = 2-NO_2. C_6H_4 ; **4c**) Ar = 3-NO_2.C_6H_4
4d) Ar = C_6H_5 ; **4e**) Ar = 2-Cl.C_6H_4 ; **4f**) Ar = 4-OCH_3.C_6H_4 ; **4g**) Ar = 2-F.C_6H_4

Scheme-1

3. Conclusion

In conclusion, we have developed a practical and novel procedure for the synthesis of substituted 3,3- dimethyl trihydro benzothiazolo[2,3-b]quinazoline-2*H*-one derivatives under monomode reactor and compared with different energy source and reactions conditions. In monomode reactor the temperature being more homogeneous and changes in the activation reactor is more efficient than the multimode reactor due to the better yield of energy obtained by microwave fascicle focalization and the more homogeneous electromagnetic field. The significant advantages offered by this procedure are operational simplicity, fast reaction, high selectivity, excellent yields of products, no reduction of other reducible functionalities, and use of no organic solvent and toxic reagent in the reaction. We believe, this reaction will find suitable applications in organic synthesis and will lead to further useful chemistry. The biological activities of synthetic libraries will be reported in due time.

4. Experimental

Melting points were determined in open glass capillaries and are uncorrected. IR spectra (KBr) were recorded on a Shimadzu FT IR–8400S spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 using $CDCl_3$ at 300.15 and 75.47 respectively. TMS was used as internal reference. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 system using sector double focus and an electron impact source with an ionizing voltage of 70 V, and with a Bruker DALTONICS APEXII, 3 Tesla, FT-ICR-MS with ESI source or EI/CI source.Purity of all compounds was checked by TLC using silica Gel 'G' coated glass plates and benzene: ethyl acetate (8 : 2) as eluent. The microwave-assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) equipped with inverter technology operating at 1000W generating 2450 MHz frequency. The monomode system was purchased from Prolabo (Synthewave 402TM, ν = 2450 MHz, $0 \leq P \leq$ 300 W) and coupled together with a microcomputer. For sake of comparison some reaction repeated in different monomode microwave reactor . The temperature of the reagents was measured by infrared pyrometry and the power of the magnetron was automatically controlled to maintain the set temperature with a proportional integral corrector. Uniform irradiation of reagents was obtained by the regular and automatic rotation of the reaction vessel. The reactors (quartz or borosilicate glass) had the following dimensions: inside diameter: 15 mm; glass thickness: 1.2 mm; maximum content: 10 cm^3. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40 kHz, 59 kHz and a nominal power 250 W; Shanghai Kudos Ultrasonic Instrument Co., Ltd.). The reaction flask was located in the cleaner, where the surface of reactants is slightly lower than the level of the water. 2-amino-6-chloro-benzothiazole was prepared by literature method.[17]

Synthesis of 9-chloro-3,3-dimethyl-6-(4′-chlorophenyl)-2,4,6-trihydro-(5H)-benzo-thiazolo [2,3-b] quinazolin-5-one (4a)

(a) Multi-component Synthesis was performed by using three different ways: (i) Conventional synthesis, (ii) Microwave-assisted synthesis and (iii) Ultrasonic irradiation.

(i) Conventional Heating- Equimolar quantities (0.01mole) of 2-amino-6-chloro-benzothiazole (1.84 gm) (**1**), 4-chlorobenzaldehyde (1.40 gm) (**2**) and dimedone (1.40 gm) (**3**) in isopropanol or n-butanol or DMF was refluxed for 42h, 40h, 15h, respectively. At the end of the reaction (monitored by TLC), the product formed in the reactions in isopropanol or n-butanol was isolated by column chromatography in silica gel (60-120 mesh), using a 1:1 mixture of chloroform and ethyl acetate as the eluent, in case of DMF, 2-propanol (5 mL) was added in reaction mixture and the precipitated product was collected to give product **4a**, which was recrystallized from ethanol.

(b) Microwave- assisted reaction.-

(i) In DMF- An equimolar mixture (0.01mole) of **1**, **2** and **3** with DMF (5ml) in a 10 ml pressure vial was placed inside the monomode reactor for 10 min (TLC) at 300W. The reaction mixture was cooled, eluted with methanol (15 ml) and poured onto crushed ice. The precipitate thus obtained was filtered, washed with water and found to be pure with no need of further purification.

Acknowledgement

We wish to thank CSIR and U.G.C. New Delhi for financial support.

References

1. Loupy, A. *Microwaves in Organic Synthesis,* 2nd Edition, (Ed); Wiley-VCH: Weinheim, 2006; (b) Loupy, A.; Petit, A..; Hamelin, J.; Texier-Boullet, F. ; Jacquault, P. ; Mathé, D. *Synthesis* **1998,** 1213. (c) Varma, R. S. *Green Chem*. **1999,** *1***,** 43; (d) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002; (e) Kappe, C.O. *Angew. Chem. Int. Ed.* **2000,** *43*, 6250.
2. Shujiang, T.; Xiaotong, Z.; Jinpeng, Z.; Jianing, X.; Yan, Z.; Qian, W.; Runhong, J.; Jiang, B.; Junyong, Z.; Changsheng, Y. *Bioorg. Med. Chem Lett.* **2006,***16,* 2925.(b) Cui, S.Li.; Lin, X.; G, Y.; Wang, F.; *J. Org. Chem.* **2005,***70*, 2866 .(c) Liu, J.F.; Ye, P.; Zhang, B.; G, Bi.; Sargent, K.; L, Yu.; Yohannes, D.; Baldino, C. M. *Org. Lett* **2005,** *70*, 6339. (d) Zhu, J.; Bienayme, H. *Multi-component Reactions;* Willey-VCH: Weinheim, Germany, 2005.
3. (a) Villemin, D.; Labiad, B. *Synth. Commun.* **1990,** *20*, 3333. (b) Bram, G.; Loupy, A.; Madjoub, M. *Tetrahedron* **1990,** *46*, 5167. (c) Villemin, D.; Alloum, A. *Synth. Commun.***1991,** *21*, 63; (d) Villemin, D.; Martin, B.; Garrigues, B. *Synth. Commun.***1993,** *23*, 2251.
4. (a) Villemin, D.; Martin, B. *J. Chem. Res.* (*S*) **1994,** 146; (b) Bram, G.; Loupy, A.; Madjoub, M.; Petit, A. *Chem. Ind.* **1991,** 396; (c) Pilard, F. J.; Klein, B.; Texier-Boullet, F.; Hamelin, J. *Synlett* **1992,** 219.
5. Nagy, G.; Filip, S.; Surducan, E.; Surducan, V. *Synth. Commun.* **1997,** *27*, 3736.
6. Souadi, A.; Hamelin, J.; Benhaoua, H. *Tetrahedron Lett.* **1998,** *39,* 4035 and cited references.
7. Diaz-Ortiz, A. ; Diez-Barra, E. ; De La Hoz, A. ; Loupy, A. ; Petit, A. ; Sanchez, L. *Heterocycles* **1994,** *38*, 795.
8. (a) Testard, A.; Loge, C.; Robert, J. M.; Lozach, O.; Blairvacq, M; Meijer, L; Thieery, V; Besson, T. *Bioorg Med. Chem. Lett.* **2006**, *16,* 3419 (b) Testard, A.; Picot, L Lazach, O; Blairvacq, M; Meijer, L; Murillo, L; Piot, J;. Thiery, M. V; Besson, T. *J. Enz. Inh. Med. Chem,* **2005**, *20*, 557 (c) Kausmeier, U.; Heinicke, J.; Arkona, C. US. Appl. 381024, 2003; US Pat 0023953, 2004; EP20010957919, 2001; EP1319010, 2003; (d) Alexandre, F.R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron Lett*. 2003**,**

44, 4455; (e) Evain, M.; Landreau, C.; Deniaud , D; Reliquet, A.; Meslin, J. C. *Acta Crystallographica Section E* **2002**, *58 (4)*, 362.

9. Wagner, G.; Bunk, E. *Pharmazie* **1979,***34*, 138.
10. Quiroga, J.; Hernandez, P.; Insuasty, B.; Abonia, R.; Cobo, J.; Sanchez, A.; Nogueras, M.; Low, J. N. *J.Chem. Soc.Perkin Trans.1***.** ***2002*****,** 555.
11. Modi, S. K.; Singh, S.; Narang, K. S. *Indian J. Chem.* **1972,***10*, 605.
12. Sharma, R. L.; Sawhney, S.; Bhatt S.; Kumari, M. *Indian J. Het. Chem.* **2002,** *11*, 117.
13. (a) Arya, K.; Dandia, A. *Letters in Organic chemistry* **2007**,*4*, 378; (b) Arya, K.; Dandia, A. *Bioorg. Med. Chem. Lett.* **2007**,*17,3298*; (c) Dandia, A.; Singh, R.; Khaturia, S. *J. Fluorine Chem***. 2007,** *125(12),* 1835; (d) Dandia, A.; Singh, R.; Khaturia, S. *Bioorg. Med. Chem*. **2006,** *14*, 1303; (e) Dandia, A.; Singh, R.; Khaturia, S. *Bioorg. Med. Chem*. **2006,** *14*, 2409; (f) Dandia, A.; Singh, R.; Sarawgi, P. *Org. Prep. Proced. Int*. **2005,** 37, 397; (g) Dandia**,** A.; Arya, K.; Sati, M.; Gautam, S. *Tetrahedron.* **2004,** *60*, 5253.
14. Pang, Y; Song, G; Dou, R. *Green Chem*. **2006,** *8*, 573; (b). Mason, T. J. *Chemistry with Ultrasound*, Elsevier, Oxford, 1990; (c). Price, G. J. *Current trends in Sonochemistry*, Royal Society of Chemistry, Cambridge, 1992.
15. Margaretha, P.; Polansky, O.E. *Montash Chem*. **1970,** *101*, 824.
16. Lipson, V. V.; Desenko, S. M.; Shirobokova, M. G.; Borodina, V. V. *Chem. Heterocycl. Compd*. **2003,** *39*, 1213.
17. Bhargava, P. N.; Baliga, B. T . *J. Indian Chem. Soc*. **1958,** *35*, 807.