Microwave Assisted Synthesis of Pyrano [2, 3-d] Pyrimidinone Derivatives

D. Nasrin*, N. Islam, F. Hoque, T. Ferdous & F. Z. Farhana
Department of Chemistry,
Bangladesh University of Engineering & Technology (BUET),
Dhaka-1000, Bangladesh
*Corresponding author: E-mail: dina@chem.buet.ac.bd

***Abstract*-- The parent barbituric acid and 2-thiobarbituric acid are convenient starting compounds for the preparation of different fused heterocycles and 5-substituted derivatives which are pharmacologically one of the most important classes of barbituric acid based compounds. The fused compounds of barbituric and thiobarbituric acid 7-(4-aminophenyl)-5-aryl-5*H*-pyrano [2, 3-d] pyrimidinone, 5a-f have been synthesized in single step by the condensation of barbituric acid/thiobarbituric acid with benzylidene/ substituted benzylidene acetophenone in glacial acetic acid in the presence of phosphorous pentoxide under microwave irradiation. The structures of the compounds were characterized by their UV, IR, ^{1}H NMR and ^{13}C NMR spectral data.**

***Index Term*-- barbituric acid, 2-thiobarbituric acid, microwave irradiation, fused heterocycle.I.**

I. INTRODUCTION

Microwave chemistry is the science of applying microwave irradiation to chemical reactions [1]-[3]. In recent years; high-speed synthesis with microwave has attracted a considerable amount of attention [4]. More than 3500 articles have been published in the area of microwave – assisted organic synthesis (MAOS) [5],[6] since the first reports on the use of microwave heating to accelerate organic chemical transformations by the group of Gedye and Giguers /Majetich [7] in 1986. In many of the published examples, microwave has been shown to dramatically reduce reaction times, increase product yield and enhance product purities by reducing unwanted side reactions compared to conventional heating method. While microwaves are both financially and energetically inexpensive to produce, the efficiency with which they can be used makes them an attractive 'green' alternative to other forms of heating. Moreover, in recent years there has been a drive within the chemical industry to reduce both the production of waste products and the use of solvents. Microwave chemistry provides a cleaner alternative, this time by exploiting the ability of microwaves to heat the reactants directly. Using only a minimum amount of solvent, the reactants are absorbed into a sponge-like support material (clays, aluminas, zeolites etc.). The reactants are then heated directly with microwaves to generate the products, which are then extracted, again with a minimum amount of solvent. As microwave heating is essentially uniform throughout the material, there is no time lost waiting for thermal conduction to heat the sample and consequently, reaction times are often measured in minutes or even seconds. The advantages of these enabling technologies have more recently also been exploited in the context of multistep total synthesis [8] and medicinal chemistry /drug discovery [9] and have additionally penetrated related field such as polymer synthesis [10], material sciences [11] nanotechnologes [12] and biochemical processes[13].

A huge literature has grown up in the field of synthesis of pharmaceutical active barbiturates and thiobarbiturates over the period of more than a century. Literature review [14] shows that extensive works have been carried out on the multifarious synthesis, structure-reactivity relationship and pharmacological activity of barbituric and thiobarbaturic acid derivatives. A large number of reports are available on the reaction of barbituric acid and thiobarbituric acid with carbonyl compounds-aldehydes, ketones and esters [15]-[17]. But it is observed that very little extent of work has been done on the reactions of barbituric acid and thiobarbiuturic acid with α,β – unsaturated carbonyl systems[18],[19]. For this purpose, in the present work, we selected a number of arylidene-*p*-aminoacetophenones as the α,β – unsaturated carbonyl system having different substituents on the aromatic rings for reaction with barbituric acid and thiobarbituric acid. Although various routes for the synthesis of the compounds have been described, the majority of them involve a number of steps and the yields are poor [20]. Therefore, it is felt necessary to develop an efficient method. In the present work we report here a one step synthesis of barbituric and thiobarbituric acid derivatives under microwave irradiation. This solvent less synthesis apart from eliminating organic solvent from work up step, also gave improved yield with reaction time reduced from hours to minutes.

II. MATERIALS AND METHODS

Melting points were determined in open capillary tubes in melting point apparatus. IR spectra were recorded on a Shimadzu FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrophotometer (400MHz) using tetramethylsilane (TMS) as internal reference. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60F-254(E. Merck), and the spots were visualized with UV light.

TABLE I
Comparison of reaction times and yields for compounds, 5a-f

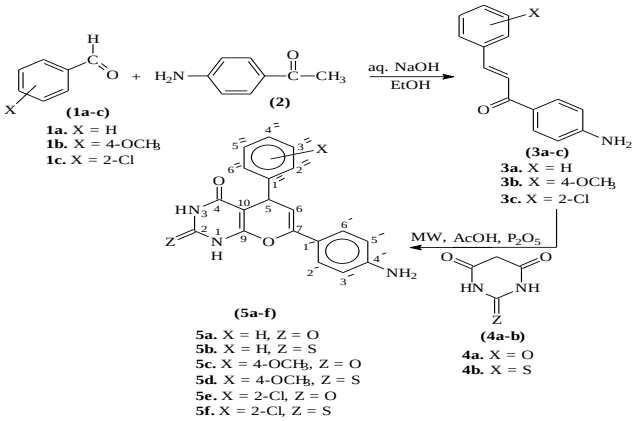
Compound	X	Z	Time (min)	Yield%
5a	H	O	5.5	87
5b	H	S	6.5	84
5c	4-OCH_3	O	7.15	81
5d	4 -OCH_3	S	7.30	80
5e	2–Cl	O	6.5	85
5f	2 –Cl	S	6.85	82

General Procedure for the Synthesis of Pyrano [2, 3-d] pyrimidinones, 5a-f:

Benzylidene/substituted benzylidene- 4-aminoacetophenones **3a-f,** were prepared from 4-aminoacetophenone (1.25 mmol) and benzaldehyde (1.25 mmol) which were dissolved in ethanol (10) in two separate conical flasks. The two solutions were allowed to mix quickly and then freshly prepared sodium hydroxide solution (5ml) were added drop wise to it. After completion the reaction followed by TLC the flask was allowed to stand overnight in refrigerator for complete precipitation. The mixture was filtered under suction on a Buchner funnel and the crude product was recrystalized from ethanol to give the pure product.
In a 50 ml ground joint flask the prepared benzylidene/ substituted benzylidene-4-aminoacetophenone (1.25 mmol) and barbituric acid/thiobarbituric acid (1.25 mmol) were dissolved in acetic acid (10ml) and P_2O_5 (0.5g). The mixture was kept in the Microwave oven with another beaker of ice. The microwave was set at 300 Watt and the time required for the completion of the reaction was 5.5-7.30 min. for the compounds, **5a-f**. The progress of the reaction was followed by TLC on silica gel plates (chloroform: n-hexane 4:1). The product from the reaction mixture solution was put to stand overnight in refrigerator for complete precipitation. The crystals were filtered under suction on a Buckner funnel and dried under vacuum pump. The crude product was recrystallized form ethanol.

7-(4-aminophenyl)-5-phenyl-5*H*-pyrano [2, 3-d] pyrimidinone, 5a:
Yield: 87% ; yellow crystal; mp 293-295^{0}C ; UV (EtOH): λ_{max} 322 nm ; IR (KBr): ν_{max} 3500.5, 3410.5, 3303.8, , 3085.5, 1676.0, 1647.1595.0, 1176.5, 1220.9, 825.5, 695.5; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ_H 9.35 (s, 2H, NH), 7.66 (d, 2H, *J*= 8.72 Hz, H-Ar), 7.33 (t, 3H, *J*= 8.52 Hz, H-Ar), 7.14 (d, 2H, *J*= 7.8 Hz, H-Ar), 6.78 (d, 2H, *J*= 8.51 Hz, H-Ar), 6.14 (d, 1H, CH, *J*=4.68 Hz), 4.27 (d, 1H, *J*=4.68 Hz), 3.50 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ_C 164.53(C-4), 163.27(C-2), 162.56(C-9), 141.45(C-7), 132.95-126.10(aromatic carbon), 137.53(C-6), 112.45(C-10), 32.34(C-5).

Scheme-1



7-(4-aminophenyl)-5-phenyl-4-oxo-2-thioxo-5*H*-pyrano [2, 3-d] pyrimidinone, 5b:

Yield: 84%; deep brown solid; m.p. 275-276°C; UV (EtOH): λ_{max} 299 nm; IR (KBr): ν_{max} 3450.6, 3310.5, 3203.6, 3085.5, 1676.9, 1652.9, 1596.9, 1220.9, 1176.5, 835.6, 685.5 cm^{-1} **;** ^{1}H NMR (400 MHz,$CDCl_3$+CD_3OD): δ_H 10.31 (s, 2H, NH), 7.91(d, 2H, *J*=8.48Hz, H-Ar),7.74(m, 3H, *J*=8.6Hz, H-Ar), 7.17(d, 2H, *J*=7.56 Hz, H-Ar), 6.24 (d,1H, *J*=4.60 Hz, H-6), 4.28 (d,1H, *J*=4.68Hz, H-5), 3.61 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ_C164.03(C-4),163.99(C-2),161.93(C-9),140.88(C-7),137.76(C-6),133.35-127.11(aromatic carbon), 113.50 (C-10), 31.87 (C-5) ppm.

7-(4-aminophenyl)-5-(4-methoxyphenyl)-5*H*-pyrano [2, 3-d]pyrimidinone, 5c:

yield 81%; yellow solid; m.p. 297-298°C; UV (EtOH): λ_{max} 251 nm; IR (KBr): ν_{max} 3455.3, 3207.5, 3070.5, 2885.5, 1728.1, 1676.0 1550.7, 1271.0, 1180.4, 805.5 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ_H 10.20 (s, 2H, NH), 7.40 (d, 2H, *J*=8.84 Hz, H-Ar), 7.29 (d, 2H, *J*=7.52 Hz, H-Ar), 6.97 (d, 2H, *J*=8.0 Hz, H-Ar), 6.75 (d, 2H, *J*=7.964 Hz, H-Ar), 6.12 (d, 1H, *J*=4.92 Hz, H-6), 4.35 (d,1H, *J*=4.6 Hz, H-5), 3.81 (s, 3H, -OCH_3), 3.55 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ_C 164.01(C-4), 163.57 (C-2), 162.24 (C-9), 141.36 (C-7), 137.55 (C-6), 155.13-130.79 (aromatic carbon),113.55 (C-10), 55.79 (-OCH_3), 32.6 (C-5) ppm.

7-(4-aminophenyl)-5-(4-methoxyphenyl-4-oxo-2-thioxo-5*H*-pyrano [2, 3-d] pyrimidinone, 5d :

yield 80%; yellow solid, m.p. 281-283°C; UV (EtOH): λ_{max} 284 nm; IR (KBr): ν_{max} 3566.1, 3544.9, 3446.6, 2985.5, 1662.5, 1654.8, 1512.1, 1249.4, 1170.5, 835.4 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ_H 10.87 (s, 2H, NH), 7.49 (d, 2H, *J*=8.48 Hz, H-Ar) 7.30 (d, 2H, *J*=8.4 Hz, H-Ar), 6.98 (d, 2H, *J*=8.12 Hz, H-Ar), 6.86 (d, 2H, *J*=8.56 Hz, H-Ar), 6.18 (d, 1H, *J*=4.68 Hz, H-6), 4.38 (d, 1H, *J*=5.2 Hz, H-5), 4.11 (s, 3H, OCH_3), 3.57 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ_C 166.41 (C-4), 163.37 (C-2), 162.24 (C-9), 143.31 (C-7), 154.13-131.55 (aromatic carbon), 135.59 (C-6), 112.49 (C-10), 53.37 (-OCH_3), 31.96 (C-5) ppm.

7-(4-aminophenyl)-5-(2-chlorophenyl)-5*H*-pyrano [2, 3-d]pyrimidinone, 5e:

yield 85%; brown solid; m.p. 279-280°C; UV (EtOH): λ_{max} 324 nm; IR (KBr): ν_{max} 3448.5, 3433.1, 3413.8, 2985.5, 1720.4, 1684.5, 1595.5, 1256.7, 1150.6, 895.5, 755.0 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ_H 10.31 (s, 2H, NH), 7.36 (d, 1H, *J*=2.32 Hz, H-Ar), 7.33 (m, 3H, *J*= 7.03 Hz, H-Ar), 7.24-7.19 (m, 4H, *J*=3.75 Hz, H-Ar), 6.36 (d, 1H, *J*=3.8 Hz, H-6), 4.79 (d, 1H, *J*=3.72 Hz, H-5), 3.59 (s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ_C 166.42 (C-4), 164.17 (C-2), 162.54 (C-9), 142.78 (C-7), 150.38-134.98

(aromatic carbon), 136.55 (C-6), 113.49 (C-10), 31.76 (C-5) ppm.

7-(4-aminophenyl)-5-(2-chlorophenyl)-4-oxo-2-thioxo-5*H*-pyrano [2, 3-d] pyrimidinone, 5f:

yield 82%; brown solid; m.p. 255-257°C; UV (EtOH): λ_{max} 322 nm; IR (KBr): ν_{max} 3315.4, 3184.3, 3107.1, 2985.5, 1678.0, 1651.0, 1531.4, 1220.9, 1178.0, 833.2, 756.0 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD): δ_H 10.99 (s, 2H, NH), 7.40 (d, 1H, *J*=8.4 Hz, H-Ar), 7.21 (t, 3H, *J*= 7.03 Hz, H-Ar), 7.13 (d, 2H, *J*=8.12 Hz, H-Ar), 6.72 (d, 2H,J=7.76, H-Ar) 5.98 (d, 1H, *J*=4.24 Hz, H-6), 4.42 (d, 1H, *J*=4.4 Hz, H-5), 3.61(s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD): δ_C 167.77 (C-4), 166.37 (C-2), 162.42 (C-9), 141.45 (C-7), 149.95-135.74 (aromatic carbon), 136.99 (C-6), 113.49 (C-10), 32.49 (C-5) ppm.

III. Results and Discussion

Compounds **5a-f** showed all expected λ_{max} (nm) values in their UV spectra .The absorption bands in the range 251-324 nm may be assigned due to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions as reported [21]-[23] previously.

The IR (KBr) data of the compounds **5a-f** showed two absorption bands at 3500.5-3315.4 cm^{-1} and 3446.6-3184.3 cm^{-1} indicate the presence of $–NH_2$ group. A sharp and broad band at 3413.8-3184.3 cm^{-1} indicates the presence of N-H group. The middle intensity vibration bands to the right (1640-1550) of the C=O absorption, caused by the N–H bending vibration. The absorption band at 1647.1-1684.5 cm^{-1} due to the conjugation of the carbonyl group with double bond. The absorption at 1728.1-1662.5 cm^{-1} was found for cyclic double bond. Absorption at 695.5-685.5 cm^{-1} indicates mono substitution of benzene ring and at 895.5-805.5 cm^{-1}indicates para substitution. Strong absorption bands at 1176.5-1180.4 cm^{-1} were also found for thiocarbonyl group and absorption bands at 1220.9-1271.0 cm^{-1} indicates the aromatic C–O bond of the compounds **5a-f**.

The ^{1}H NMR spectrum of the compounds **5a-f** showed the peak at δ_H 9.35-10.99 (s, 2H, -NH-) due to the N–H protons in the compound which were strongly deshielded and appeared as singlet in the ^{1}H NMR spectrum. The aromatic protons of the compounds **5a-f** showed chemical shift at δ_H 6.72-7.91 in their nmr spectrum. The chemical shift at δ_H 5.98-6.36 were found as a doublet with *J* value 3.8-4.92 Hz for the protons 6-H of the compounds **5a-f**.The 5-H protons of the compounds showed the chemical shift at δ_H 4.27-4.79 as a doublet with *J* value 4.4-5.2 Hz in their nmr spectrum. The chemical shift found at δ_H 3.50-3.61 as a singlet was due to the NH_2 protons. The $–OCH_3$ protons showed the chemical shift at δ_H 3.81-4.11 as a singlet in there spectrum.

The ^{13}C NMR spectrum of the compounds **5a-f** showed the peak at δ_C 164.03-167.77 for C-4, at δ_C 163.27-166.37 for C-2 and at δ_C 161.93-162.56 for C-9 carbon which were strongly deshielded. The chemical shift at δ_C 140.88-143.31 represents the C-7 and at δ_C 135.59-137.76 represents the C-6 carbon. The aromatic carbons showed the peaks at δ_C 126.10-155.1 in their nmr spectrum. The peak at δ_C 112.45-113.50 of the compounds **5a-f** represents C-10. The peak at δ_C 31.76-32.60 was found for the compounds due to the C-5 carbon and the peak at δ_C 55.79-53.37 was found due to the $–OCH_3$ carbons

IV. Conclusions

With the starting materials **3a-c,** a series of the fused compounds of barbituric and thiobarbituric acid 7-(4-aminophenyl)-5-aryl-*5H*-pyrano [2, 3-d] pyrimidinone, **5a-f** were synthesized in aqueous ethanol. All reactions were carried out in a microwave oven with special fabricated glassware and optimum reaction conditions were determined. These synthesis apart from reducing the use of organic solvents from work up step, also gave improved yield as compared to the conventional heating with reaction time reduced from hours to minutes. Low amount of chemicals were used making the method of synthesis environmental friendly. In other words this modest work was a part of 'Green chemistry' too.

V. Acknowledgment

Financial support by the Bangladesh University of Engineering and Technology (BUET), Dhaka is gratefully acknowledged. I am also grateful to the Department of Chemistry to give me an opportunity to undergo M. Phil. Program.

VI. References

[1] K.K. Canon, *Jpn. Kokai Tokkyo koho-JP* vol. 776, 1983, pp. 58138.
[2] J. D. Kendal and G.F. Duffin, US Patent 2640056, 1953.
[3] J. D. Kendal and G.F. Duffin, US Patent 2639990, 1952.
[4] D. Adam, *Nature*, vol. 421, 2003, pp. 571-572.
[5] A.Loupy, "*Microwaves in Organic Synthesis"*, ed. Wiley-VCH, Weinheim, 2002; P. Lidström and J.P.Tierney "*Microwave Assisted Organic Synthesis"*, Blackwell Publishing, Oxford, 2005.
[6] R. A. Abramovitch, "*Organic Preparations and procedures International"*, vol. 23, 1991, 685-711. ; S. Caddick, *Tetrahedron*, vol. 51, 1995, pp.10403-l0432.; P. Lidstrom, J. Tierney, B. Wathey, and K. Westman, *J. Tetrahedron*, vol. 57, 2001, pp. 9225-9283.
[7] R. Gedye, F. Smith, K. Westman, H. Ali, , L. Baldisera, L. Laberge, and J. Rousell, *Tetrahedron*
[8] *Letters*, vol. 27, 1986, pp. 279-282; R. J. Giguere, T. L Bray, S. M. Duncan and G. Majetich, *Tetrahedron Letters*, vol. 27, 1986, pp. 4945-4948.
[9] I. R. Baxendale, S.V. Ley, M. Nessi, and C. Piutti, *Tetrahedron*, 58, pp. 2002, 6285-6304; D. D. Artman, A. W. Grubbs, and R. M. Wi1liams, *Journal of the American Chemical Society*, vol.129, 2007, pp.6336–6342; P. Appukkuttan, and E. Van der Eycken, *Topics in Current Chemistry*, vol. 266, 2006,1-47.
[10] J. L. Krstenansky, and I. Cotterill, *Current Opinion in Drug Discovery & Development*, vol.4, 2000, pp. 454-461; M. Larhed, and A. Hallberg, *Drug Discovery Today*, vol. 6, 2001, pp. 406–416.
[11] D. Bogdal, P. Penczek, J. Pielichowski, and A. Prociak, *Advances in Polymer Science*, vol. 163, 2003, pp. 193–26; F. Wiesbrock, R. Hoogenboom, and U. S. Schubert, *Macromolecular Rapid Communications*, vol. 25, 2004, pp.1739–1764.
[12] S. Barlow, and S. R. Marder, *Advanced Functional Materials*, vol. 13, 2003, pp. 517-518; Y.J. Zhu., W.W. Wang, R-J. Qi, and X.-L. Hu, *Ange. Chem. Int.l Ed*, vol. 43, 2004, pp. 1410–1414.
[13] M. Tsuji, M. Hashitnoto, Y. Nishizawa, M. Kubokawa, and T. Tsuji, *Chemistry –A European Journal*, vol. 11, 2005, pp. 440-452.
[14] J. M. Collins, and N. E. Leadbeater, *Organic and Biomolecular Chemistry*, vol. 5, 2007, pp. 1141–1150; J. R. Lill, E, S. Ingle, P. S. Liu, V. Pham, and W. N. Sandoval, *Mass Spectrometry Reviews*, vol. 26, 2007, pp. 657-671.

[15] R. Y. Levina and F. K. Velichko, *Russ. Chem. Rev*. (Eng. Transl.) vol. 29, 1960, pp. 437.
[16] J. T. Bojarski, J. L. Mokrosz, H. J. Barton and M. H. Paluchowaka, *Advances in Heterocyclic* (Review Article), vol. 38, 1985, pp. 229-297.
[17] Shamsunnahar, *M. Phil thesis*, University of Dhaka, Dhaka-1000, 1999.
[18] S. Mosaddeq Ahmed, *Ph.D. Thesis*, University of Dhaka, Dhaka-1000, 2003.
[19] A. N. Osman, M. M. Kandeel, M. M. Said and E. M. Ahmed. *Indian J. Chem.* Vol. 35B (10), 1996, 1078.
[20] L. P. Zalukayev and V. L. Trostyanetskaya., *Khim. Geterotsiki. Soedin.* 1971, p.836.
[21] V. K. Ahluwalia, R. Aggarwal and R. Kumar., *Indian J. Chem.* Vol. 32B, 1993, pp. 963-964.
[22] J. T. Bojarski, J. L.Mokrosz, H. J. Barton and M. H. Paluchowaka, *Advances in Heterocyclic Chem.* vol. 38,1985, p. 229.
[23] A. N. Osman, M. M. Kandeel, M. M. Said and E. M. Ahmed, *Indian J. Chem.*, Vol. 35B (10), 1996, p.1073.
[24] M. G. Ahmed, S. A. Ahmed, S. M. Ahmed, A. Hussam and M. M. Hossain, *J. Chem . Res.*,vol.10, 2005, p.622.