Short Communication

Ecofriendly Synthesis of Novel Antifungal (Thio)Barbituric Acid Derivatives

Mazaahir Kidwai,* Ruby Thakur, and Richa Mohan

Department of Chemistry, University of Delhi, Delhi-110007, India
E-mail: kidwai_chemistry@yahoo.co.uk; Fax: (91 11) 27666235

Received 17-07-2004

Abstract

An expeditious solventless synthesis of novel Mannich bases of thiobarbiturates and barbiturates using montmorillonite clay under microwaves are herein described. This methodology eliminates the use of excess of solvent during the course of reaction. The reaction time is brought down from hours to minutes along with yield enhancement. The rate enhancement and high yield is attributed to the coupling of MWS with solventless conditions. Further, the role of montmorillonite K-10 clay is studied in the reaction and it is concluded that microwave assisted montmorillonite clay catalyzed reaction is the best in terms of catalysis as well as reaction and yield. All the compounds synthesized were screened for their antifungal activity against A. niger and A. flavus and found to possess good activity.

Key words: Thiobarbiturates, Barbiturates, Mannich base, Montmorillonite, Microwave, Antifungal

Introduction

Mannich reaction is widely used for the construction of nitrogen containing molecule.[1] In this three component transformation, compounds possessing β-hydrogen atom, an aldehyde and an amine react to form β-aminoketone derivatives. In addition it has been reported[2] that insertion of aryl amino methyl moiety at 5th-position of TBA/BA enhances the antidepressant activities of the resultant compounds. Best example of the heterocycles containing active methylene group is TBA/BA. Several Mannich bases possess diverse biological activities viz. antimicrobial,[3] antitubercular and antiviral activities.[4] Also TBA and BA derivatives are well known to possess antibacterial,[5] sedatives,[6] herbicides,[7] fungicides[8] and antiviral agents.[9]

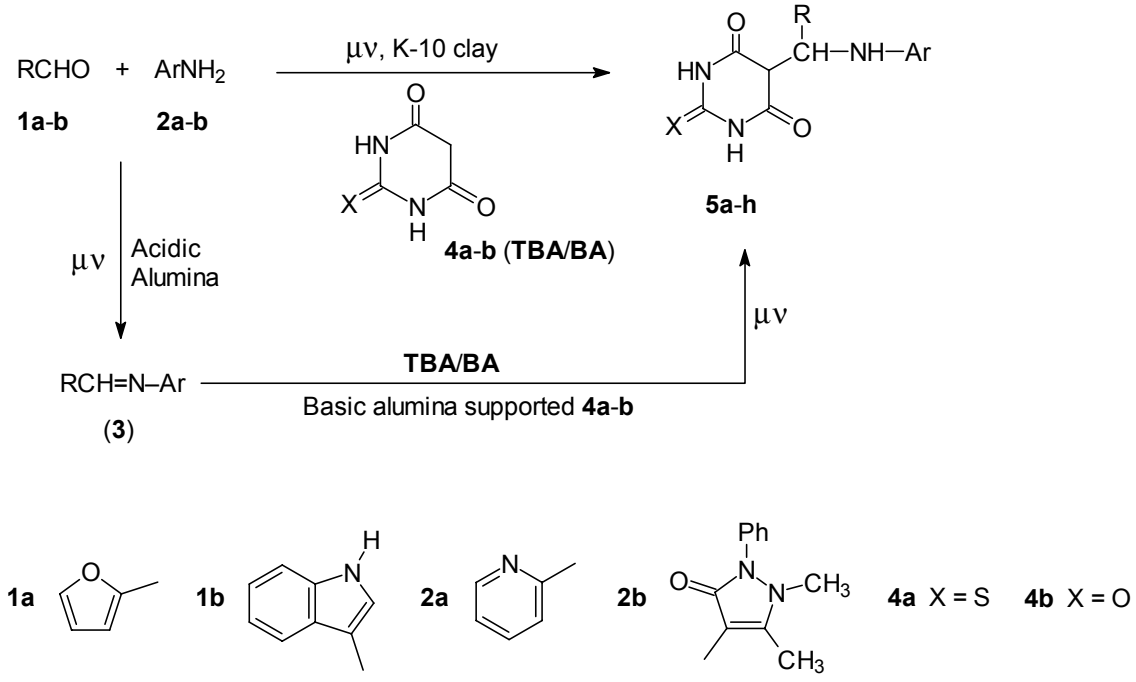
The coupling of microwave irradiation (MWI) with solid supported reagents is well known for the synthesis of variety of compounds[10–16] where in chemical reaction are accelerated because of selective adsorption of microwaves by the polar molecules. Montmorillonite clay, a class of inexpensive and non-corrosive solid acids, has reacted great development in different areas of organic synthesis[17–18] due to their environmental compatibility. These dry media reactions[19–21] catalyzed by montmorillonite clay, under microwave activation results in unique chemical processes with special attribute such as enhanced reaction rate, higher yield, greater selectivity and ease of manipulation.

In the view of above mentioned biological activity of thiobarbiturates and Mannich bases and in continuation of our interest in the development of environmentally benign protocols,[22–24] we herein report, a facile, rapid, one pot synthesis of *N*-pyridyl/*N*-antipyryl-1-furyl/indolyl-1-[thiobarbituric acid/barbituric acid]aminomethane (**5a–h**) using montmorillonite clay in dry media under MWI. Moreover, novel reactions were also performed using NaOEt in ethanol and glacial acetic acid under conventional heating, and we developed a new synthetic procedure for the synthesis of (thio)barbituric acid derivatives. These derivatives were screened for their antifungal activity against *A. niger* and *A. flavus* (Table 2).

Results and Discussion

Condensation of Aldehyde **1** with amine **2** in the presence of glacial acetic acid (Method C) with ethanol as solvent was carried out under conventional heating. On formation of intermediate **3**, TBA/BA **4** dissolved in NaOEt solution was added to it. The final product **5a–h** was obtained in 10–12 hrs of heating with moderate yield. In an attempt to "greenfiy" the synthetic procedure and increase its rate and yield experiments were done under microwaves (MWs).

Aldehyde **1a–b** and amine **2a–b** was reacted with TBA/BA over montmorillonite K-10 clay[25b] under MWI to give Mannich reaction products **5a–h** at C-5 position of TBA/BA (Method A, Scheme 1). The structural assignment of **5a–h** is based on elemental analysis and



Scheme 1. Microwave assisted synthesis of thiobarbituric acid and barbituric acid derivatives using different solid supports.

spectroscopic data. The molecular formulae were confirmed by elemental analysis. In ^{1}H NMR the appearance of doublet at 3.0–3.8 due to C–H group introduced by Mannich reaction was observed. Also broad signal at δ 4.9–5.2 and doublet at δ 4.5–4.8 due to N–H and C_5-H of TBA/BA respectively of the synthesized compounds **5a–h** in ^{1}H NMR spectra confirmed the formation of products **5a–h**.

In order to study the versatility of different solid support and on observing the fact that aldehyde reacts with amine in acidic condition. The reaction was also tried with acidic alumina[25a] (Method B, Scheme 1). Upon formation of intermediate, TBA/BA adsorbed separately over basic alumina[25c] was added to the above reaction bath without eluting the intermediate in between. Now the resulting reaction mixture was subjected to microwaves, final product **5a–h**, so obtained was in good yield (Table 1).

Reactions between **1**, **2**, and **4** under conventional heating (Method C) were completed in 10–12 hrs with moderate yield (Table 1), whereas the same reactions under MWs (Method A and B) gave excellent yield with in few minutes of irradiation. Further, on moving from two pot, alumina supported (Method B) synthesis, to the reactions catalyzed by montmorillonite K-10 clay (Method A), we observed reduction in reaction time and improvement in yield (Table 1). This result can be attributed to the ditopic nature[23b] of montmorillonite K-10 clay.

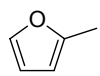
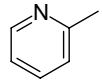
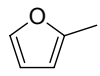
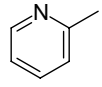
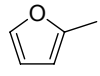
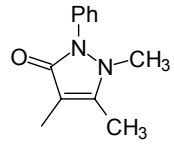
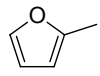
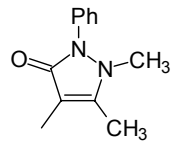
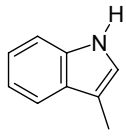
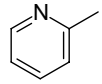
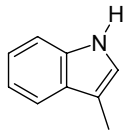
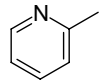
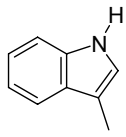
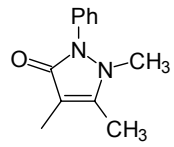
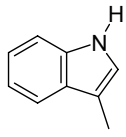
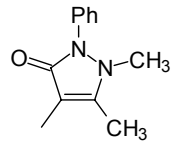
All compounds synthesized were screened for their antifungal activity against *A. niger* and *A. flavus* by paper disc diffusion method.[19] The zone of inhibition was measured in millimeters. The antifungal activities of the test compounds were compared to standard salicylic acid[20] (17–21 mm). DMF was used as solvent. All compounds have shown good activity against both fungi. However, thiobarbituric acid derivatives **5a**, **5c**, and **5g** have shown excellent antifungal activity (20–22 mm) against both *A. niger* and *A. flavus*. Compounds **5b**, **5f** showed better activity (16–18 mm) against *A. niger* as compared to activity (11–13 mm) against *A. flavus* (Table 2).

Table 2. Antifungal activity of compounds (**5a–h**).

Compound	Inhibition of *A. niger* (50 μg/mL)	Inhibition of *A. flavus* (50 μg/mL)
5a	+++++	+++++
5b	++++	+++
5c	+++++	+++++
5d	+++	++
5e	++++	+++
5f	++++	+++
5g	+++++	+++++
5h	+++	++++
Salicylic acid	+++++	++++++

+ : 3–9 mm; ++ : 10–12 mm; +++ : 13–15 mm; ++++ : 16–21 mm; +++++ : >21 mm.

Table 1. Comparison of reaction times and yields for compounds **5a–h.**

Compound	X	R	Ar	Method A Time (min'sec")/Yield (%)	Method B[b] Time (min'sec")/Yield (%)	Method C (hr.min')/Yield (%)
5a	S			4'50"/96	14'/85	10.20'/65
5b	O			3'40"/94	12'/85	11.10'/62
5c	S			3'20"/97	11'/81	10.30'/66
5d	O			3'50"/95	9'/79	11.30/58
5e	S			3'40"/95	8'/82	10.40'/59
5f	O			3'20"/92	7'50"/88	10.10'/61
5g	S			4'30"/97	10'20"/84	12.20'/56
5h	O			3'50"/91	10'50"/83	12.40'/54

[b] Total time for the synthesis (5+x) min, 5 min is the time required for the synthesis of intermediate **3** over acidic alumina. 'X' is the additional time required for the synthesis of **5a–h** from intermediate **3**.

Conclusions

In conclusion we have modified and developed a facile and convenient synthetic procedure for preparation of novel Mannich bases (β-amino ketone derivative) of thio(barbiturates) by coupling microwaves with motmorillonite K-10 clay. The procedure clearly highlights the versatility of solid supports when coupled with microwaves. The advantages of this ecofriendly and safe protocol include a simple reaction set up, good product yield, short reaction time and above all the use of volatile and toxic solvents is eliminated. All the compounds synthesized were found to possess good antifungal activity.

Experimental Section

Melting points were determined by Electrothermal melting point apparatus and are uncorrected.

IR spectra (in KBr) were recorded on 1710 Perkin Elmer FT infrared spectrophotometer. ^{1}H NMR spectra were recorded on FT NMR Hitachi R-600 (60 MHz) spectrometer. Elemental Analyses were performed on Hareaus CHN-Rapid Analyser. For microwave irradiation (MWI) Kenstar microwave oven, Model No. OM9925E (2450 MHz, 800 W) was used. The purity of the compounds was checked on silica gel coated Al plates (Merck). The approximate temperature of the reaction mixture (as measured by AZ, mini Non-Contact Infrared Thermometer, Model No. 8868), was 90–120 °C (800 W).

General Procedure for the Synthesis of *N*-pyridyl/*N*-antipyryl-1-furyl/indolyl-1-[thiobarbituric acid/barbituric acid]aminomethane (5a–h). Method A:

Montmorillonite K-10 clay[25b] 18 g was added to the equimolar mixture of **1a–b** (0.01 mol), **2a–b** (0.01 mol) and **4a–b** (0.01 mole) in ethanol. The reaction mixture was stirred well and dried in air. Then the reaction mixture was placed in alumina bath[26] inside the microwave oven at 560 W for 3.2–4.5 minutes. Progress of the reaction was monitored through TLC at the interval of 30 sec. On completion of the reaction, mixture was cooled at room temperature the product was extracted using ethanol and solvent was removed under reduced pressure, which yield the corresponding title compounds **5a–h**, which were recrystallized from the appropriate solvents.

Method B:

Acidic alumina[25a] was added to the equimolar mixture of **1** and **2** (0.01 mol) in ethanol. The reaction mixture was stirred well, dried in air and placed in alumina bath[26] inside the microwave oven for 5 min on formation of intermediate **3** as checked by TLC examination, another reactant **4a–b** which was already adsorbed over basic alumina[25c] was added to the above reaction bath without eluting the intermediate in between. Now the resulting reaction mixture **3** and **4a–b** formed were again irradiated under microwaves for specified time. Progress of reaction was monitored through TLC at the interval of 30 sec. On completion of reaction, mixture was cooled at room temperature the product was extracted using ethanol and solvent was removed under pressure. The final product **5a–h** so obtained was recrystallized using appropriate solvent.

Method C:

An equimolar amount of **1** and **2** (0.01 mol) were put in a round-bottomed flask. To this, glacial acetic acid in ethanol was added and the reaction mixture is refluxed for 30 min gently with stirring on a magnetic stirrer equipped with an air condenser. Then, on formation of intermediate **3** as checked by TLC examination, another reactant **4** dissolved in NaOEt in EtOH was added to the above reaction mixture and refluxed for 10–12 hr. On formation of product as monitored by TLC the product was filtered through Hirsch Funnel and the solid so obtained was recrystallized with the appropriate solvent.

5a: Mp 295–296 °C (Petroleum ether). ^{1}H NMR ($CDCl_3$+DMSO) δ 8.1–8.5 (m, 5H, C-H-pyridine), 4.5–4.8 (d, 1H, *J* 7.5 Hz, C_5HTBA), 5.0 (brs, 1H, NH), 6.2–6.4 (m, 3H, C-H furan ring), 3.0 (d, 1H, *J* 7.4 Hz, C-H). IR (KBr): 1030 (C=S), 1600 (C=C), 1650 (C=O), 2960 (C-H), 3050 (Py C-H), 3390 (N-H) cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_4O_3S$: C 53.33, H 3.49, N 17.77. Found: C 53.35, H 3.48, N 17.79.

5b: Mp 252–253 °C (Methanol). ^{1}H NMR ($CDCl_3$+DMSO) δ 8.1–8.5 (m, 5H, C-H-pyridine), 4.5–4.8 (d, 1H, *J* 7.8 Hz, C_5HBA), 5.2 (brs, 1H, NH), 6.2–6.4 (m, 3H, C-H furan), 3.1 (d, 1H, *J* 7.8 Hz, CH). IR (KBr): 1650 (C=O), 2960 (C-H), 3050 (Py C-H), 3320 (N-H) cm^{-1}. Anal. Calcd for $C_{14}H_{11}N_4O_4$: C 56.18, H 3.67, N 18.72. Found: C 56.16, H 3.65, N 18.71.

5c: Mp 310–311 °C (Petroleum ether). ^{1}H NMR ($CDCl_3$+DMSO) δ 2.0 (s, 3H, CH_3), 2.6 (s, 3H, NCH_3), 7.8 (m, 5H, N-Ph), 4.9 (brs, 1H, NH), 6.2–6.4 (m, 3H, CH furan), 4.7–4.8 (d, 1H, *J* 8.0 Hz, C_5HTBA), 3.2 (d, 1H, *J* 7.9 Hz, C-H). IR (KBr): 1030 (C=S), 1550 (C=O antipyrine), 1630 (C=C antipyrine), 1650 (C=O), 3340 (N-H) cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_5O_4S$: C 56.47, H 4.47, N 16.47. Found: C 56.45, H 4.45, N 16.45.

5d: Mp 302–303 °C (Ethanol). ^{1}H NMR ($CDCl_3$+DMSO) δ 2.1 (s, 3H, CH_3), 2.5 (s, 3H, NCH_3), 7.8 (m, 5H, N-Ph), 5.1 (brs, 1H, NH), 6.2–6.4 (m, 3H, C-H furan), 4.7–4.9 (d, 1H, *J* 8.1 Hz, C_5HBA), 3.0 (d, 1H, *J* 8.0 Hz, C-H). IR (KBr): 1550 (C=O antipyrine), 1630 (C=C antipyrine), 1650 (C=O), 3340 (N-H) cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_5O_5$: C 58.67, H 4.64, N 17.18. Found: C 58.69, H 4.66, N 17.19.

5e: Mp 286–287 °C (Chloroform). ^{1}H NMR ($CDCl_3$+DMSO) δ 5.2 (brs, 1H, NH), 4.6–4.8 (d, 1H, *J* 7.6 Hz, C_5HTBA), 7.0–7.2 (NH-indole), 8.1–8.5 (s, 1H, C_6Hpyridine), 6.7–6.9 (d, 1H, *J* 1.5 Hz, C_5Hpyridine), 6.5 (s, 1H, C_2Hindole), 3.4 (d, 1H, C-H). IR (KBr): 1030 (C=S), 1650 (C=O), 2960 (C-H), 3050 (Py-C-H), 3390 (N-H) cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_5O_2S$: C 59.34, H 3.84, N 19.23. Found: C 59.36, H 3.86, N 19.26.

5f: Mp 293–294 °C (Methanol). ^{1}H NMR ($CDCl_3$+DMSO) δ 5.2 (brs, 1H, NH), 7.0–7.2 (NH-indole), 8.1–8.5 (s, 1H, C_6Hpyridine), 6.7–6.9 (d, 2H, *J* 1.5 Hz, C_5Hpyridine), 6.5 (s, 1H, C_2Hindole), 4.8–4.9 (d, 1H, *J* 7.6 Hz, C_5HBA), 3.8 (d, 1H, *J* 7.5 Hz, C-H). IR (KBr): 1640 (C=O), 2950 (C-H), 3040 (Py-C-H),

3390 (N-H) cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_5O_3$: C 62.06, H 4.02, N 20.11. Found: C 62.09, H 4.06, N 20.14.

5g: Mp 264–265 °C (Petroleum ether). ^{1}H NMR ($CDCl_3$+DMSO) δ 2.1 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.8 (m, 5H, NPh), 5.0 (brs, 1H, NH), 7.0–7.2 (N-H indole), 6.5 (s, 1H, C_2Hindole), 4.3–4.5 (d, 1H, *J* 8.2 Hz, C_5HTBA), 3.4–3.5 (d, 1H, *J* 8.1 Hz, C-H). IR (KBr): 1030 (C=S), 1550 (C=O antipyrine), 1630 (C=C antipyrine), 1640 (C=O), 3370 (N-H) cm^{-1}. Anal. Calcd for $C_{14}H_{22}N_5O_3S$: C 62.06, H 4.78, N 15.21. Found: C 62.64, H 4.79, N 15.24.

5h: Mp 154–155 °C (Ethanol). ^{1}H NMR ($CDCl_3$+DMSO) δ 2.1 (s, 3H, CH_3), 2.5 (s, 3H, NCH_3), 7.8 (m, 5H, NPh), 5.0 (brs, 1H, NH), 7.0–7.2 (N-H indole), 6.5 (s, 1H, C_2Hindole), 4.1–4.2 (d, 1H, *J* 7.7 Hz, C_5HBA), 3.6–3.8 (d, 1H, *J* 7.6 Hz, C-H). IR (KBr): 1550 (C=O antipyrine), 1630 (C=C antipyrine), 1640 (C=O), 2960 (C-H), 3350 (N-H) cm^{-1}. Anal. Calcd for $C_{24}H_{22}N_5O_4$: C 64.86, H 4.25, N 15.76. Found: C 64.82, H 4.93, N 15.74.

Acknowledgements

Authors are thankful to the University Grants Commission, New Delhi for their financial assistance.

References

1. M. Arend, B. Westermanm, N. Risch, *Angew. Chem., Int. Ed.* **1998**, *37*, 1045–1070.
2. V. Singh, R. Khanna, V. K. Srivastava, G. Palit, K. Shanker, *Arzneim–Forsch.* **1992**, *42*, 277–280.
3. P. Y. Shirodkar, M. M. Vartak, *Indian J. Het. Chem.* **2000**, *9*, 239–240.
4. N. K. Ralhan, H. S. Sachdev, *J. Sci. Ind. Res.* **1960**, *19*, 215–218.
5. L. K. Akopyan, A. S. Adzhibekyan, G. A. Porkinyan, E. A. Tumasyan, *Bilzh. Arm.* **1976**, *29*, 80; *Chem. Abstr.* **1976**, *85*, 72068.
6. S. Senda, H. Fugimura, H. Izumi, *Japan Patent* 193,6824, **1968**; *Chem. Abstr.* **1969**, *70*, 78001.
7. S. L. Katz, A. W. Gay, *U.S. Patent* 352,806, **1982**; *Chem. Abstr.*, **1983**, *98*, 215603.
8. W. G. Brouwer, E. E. Felauerand, A. R. Bell, *U.S. Patent* 779,982, **1990**; *Chem. Abstr.* **1991**, *114*, 185539.
9. A. Esanu, *BE Patent* 902,232, **1985**; *Chem. Abstr.* **1986**, *104*, 130223.
10. P. Hermkens, H. Ottenheijm, D. Rees, *Tetrahedron* **1997**, *53*, 5643–5678.
11. J. Rebek, D. Brown, S. J. Zimmerman, *J. Am. Chem. Soc.* **1975**, *97*, 454–455.
12. R. S. Varma, *Green Chemistry* **1999**, *1*, 43–55.
13. M. Kidwai, R. Venkataramanan, R. K. Garg, K. R. Bhushan, *J. Chem. Res. (S)* **2000**, 586–587.
14. M. Kidwai, P. Misra, *Synth. Commun.* **1999**, *29*, 3237–3250.
15. M. Kidwai, P. Misra, K. R. Bhushan, *Synth. Commun.* **2001**, *31*, 19–24.
16. M. Kidwai, P. Sapra, K. R. Bhushan, P. Misra, *Synthesis* **2001**, *10*, 1509–1512.
17. T. S. Li, A. X. Li, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913–1915.
18. P. K. Ramchandani, B. S. Upnade, M. P. Vinod, R. D. Wakharkar, V. R. Choudhary, A. Sudalai, *Chem. Commun.* **1997**, 2071–2072.
19. (a) K. Smith, Ed., *Solid Supports and Catalysis in Organic Synthesis*, Ellis Horwood, PTR Prentice Hall: Chichester, 1992. (b) J. H. Clark, *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH: Weinheim, 1994.
20. R. S. Varma, R. K. Saini, *Tetrahedron Lett.* **1997**, *38*, 2623–2624.
21. D. Villemin, A. B. Alloumn, *Synth. Commun.* **1991**, *21*, 63–68.
22. M. Kidwai, *Pure & Applied Chemistry* **2001**, *73*, 147–151.
23. (a) M. Kidwai, P. Sapra, *Synth. Commun.* **2002**, *32*, 1639–1645. (b) M. Kidwai, R. Venkataramanan, B. Dave, *Synth. Commun.* **2002**, *32*, 2161–2168.
24. (a) M. Kidwai, R. Venkataramanan, B. Dave, *Green Chemistry* **2001**, *3*, 278–279. (b) M. Kidwai, S. Rastogi, R. Venkataramanan, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 203–204. (c) M. Kidwai, A. D. Mishra, *J. Serb. Chem. Soc.* **2004**, *69*, 247–254.
25. (a) Aluminium oxide acidic, Brockmann I (~150 mesh, 58 Å, CAMAG 506–C–1, surface area 155 m^2/g) was used. (b) Montmorillonite K-10: K-Catalyst, 69866 Fluker, Surface; 200 ± 20 m^2/g. (c) Aluminium oxide, Brockmann I (Aldrich Chem. Co., Cat. No. 19, 944–3 ~150 mesh 58 Å, Surface area 155 m^2/g).
26. G. Bram, A. Loopy, M. Majdoub, *Tetrahedron* **1990**, *46*, 5167.

Povzetek

Opisana je sinteza novih Mannichovih baz iz barbituratov in tiobarbituratov s pomočjo montmorillonita in mikrovalov. Sintesa je hitra in poteka brez topil. Ta metoda, v primerjavi s klasičnim segrevanjem, zmanjša reakcijske čase iz ur na minute, povečani pa so tudi izkoristki. Vsem pripravljenim spojinam smo testirali aktivnost na *A. niger* in *A. flavus*.