STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, XLV, 2, TOM I, 2010

Dedicated to the memory of Prof. dr. Ioan Silaghi-Dumitrescu marking 60 years from his birth

MICROWAVES ASSSITED *N*-ALKYLATION OF PHENOTHIAZINE

LUIZA GĂINĂ, TIMEA DALLOS, CASTELIA CRISTEA[*], TAMAS LOVASZ, IANI PERETEANU, MIHAI SURDUCAN AND LUMINIȚA SILAGHI-DUMITRESCU

ABSTRACT. A *green chemistry* approach to the N-alkylation of phenothiazine is described. The chemical process was improved by applying the microwave assisted heating technique in closed vessel and by using safer solvents such as alcohol or PEG. Reaction conditions were optimized to give good yields in short reaction times.

Keywords: *Phenothiazine, N-alkylation, MAOS, green chemistry*

INTRODUCTION

N-alkyl-phenothiazine derivatives, proved to be extremely usefull substrates for the regioselective preparation of C-substituted phenothiazine derivatives *via* direct aromatic electrophilic substitution as well as by using organometallic intermediates [1-6]. N-methyl- and 10-ethylphenothiazines were prepared right at the begining of the phenothiazine chemistry by using the corresponding alcohols as alkylating agents [7] and the seeking for improved reaction conditions never stopped ever since. In alkaline conditions, alkyl halides proved to be excellent alkylating agents and large scale application were developed for the preparation of neuroleptic drugs containing this pharmacophore unit [8]. DMS [9] and oxalic acid esters [10] were also reported as alkylating agents.

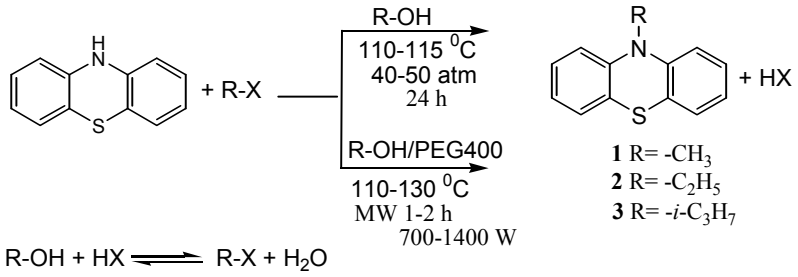
The tremendous development of microwave assisted organic synthesis (MAOS) during the last decades is supported by certain advantages such as: reaction rate acceleration, milder reaction conditions, lower energy input, usually higher reaction yields and sometimes different selectivity, which were observed after microwave irradiation, as compared to conventional convective heating of the reaction mixtures [11,12]. These advantages successfully integrate *MAOS* into the *green chemistry* principles, seeking for the development of cleaner, environmentally benign and energy efficient processes [13].

[*] *Universitatea Babeş-Bolyai, Facultatea de Chimie şi Inginerie Chimică, Str. Kogălniceanu Nr. 1, RO-400084 Cluj-Napoca, Romania, castelia@chem.ubbcluj.ro*

The aim of this work is to describe our contribution to the improvment of the reaction conditions applied for the *N*-alkylation of phenothiazine with alkyl-halides, based on *green chemistry* principles and new technical possibilities offered by the use of modern *on-line* controlled microwave assisted reactors.

RESULTS AND DISCUSSION

A mixture of alkyl iodide and alcohol gave good yields of *N*-alkyl phenothiazine, when the reaction was performed at high temperatures (110-120 ^{0}C) in closed vessels (scheme 1). A volatile alcohol develops high internal pressures and may also participate to the *in situ* regeneration of alkyl iodide and for these reasons both the alkyl halide and the alcohol should contain the same alkyl chain. In these conditions, *N*-methyl-phenothiazine **1** was obtained more than 70% yield by using a mixture of methyl iodide and methanol, while a mixture of ethyl iodide and ethanol gave *N*-ethyl-phenothiazine **2** in lower yields (50-70%) [14,15]. 24 Hours of heating were required to complete these reactions and longer alkyl chains could not be attached to the heterocyclic nitrogen atom under these circumstances.



Scheme 1

Particularly efficient heating processes induced by the dielectric heating afforded shorter reaction times for the alkylation of phenothiazine with methyl iodide, ethyl iodide and *i*-propyl bromide respectively, in the presence of the proper alcohol, which is a solvent with medium absorbing properties of the microwave radiation (scheme 1). As it can be seen from table 1 which summarises the results obtained when different reaction conditions were applied, the best results were obtained when the corresponding alcohol was employed. Even though the recorded yields were decreasing with the increase of the alkyl chain, N-*i*-propyl-phenothiazine **3** could be obtained in 56% yields using an alkylating mixture of *i*-propyl bromide and isopropanol after 40 minutes of high power irradiation.

In our survey for safer solvents we selected PEG, a solvent capable to efficiently absorb microwave energy and thus to ensure a rapid heating of the reaction mixture by dipolar polarization mechanism.

However, as it can be seen in table 1, the yields in the methylation reaction were not improved neither when a mixture of alcohol and PEG (v/v 1:1), nor PEG was employed. Satisfactory yields were generated when catalytic amounts of were added Cs_2CO_3 to the PEG containing reaction mixture.

Table 1. Experimental conditions employed for the microwave assisted alkylation of phenothiazine with alkylhalides

Cpd	Solvent v/v	$Temp_{max}$ [^{0}C]	Power/time [W]/[min]	Yield %
1	MeOH	110	800W/20 min 1000W/90 min	79
	PEG400/CH_3OH 1/1	110	800W/20 min , 1000W/60 min	20
	PEG400	110	800W/20 min, 1000W/60 min	16
	n-BuOH, Cs_2CO_3	130	700W/1 min 800W/15 min	49
	PEG400 Cs_2CO_3	125	700W/2 min 800W/60 min	44
	BuOH, H_2O, Aliquat 336, KOH	130	700W/90 min, 800W/15 min	43
2	EtOH		800W/20 min 1000W90 min	65
	PEG400/EtOH, 1/1	140	500W/40 min 800W/30 min	54
	PEG400	130	800W/2 min 500W/60 min	17
3	*i*-PrOH	130	1400W/40 min	56
	PEG400, Cs_2CO_3	120	700W/2 min 800 W/60 min	10

Microwave irradiation was applied for the methylation of phenothiazine with methyl iodide under phase transfer catalysis conditions (using PTC catalyst Aliquat 336, butanol solvent and KOH base). Satisfactory yields were obtained in much shorter reaction time, as compared to classical PTC experiment which typically requires 48-72 hours of vigorous stirring.

CONCLUSIONS

MAOS can be successfully applied to the preparation of N-alkyl-phenothiazine with the advantage of a much shorter reaction time required in order to obtain comparable reaction yields with those resulted under conductive heating conditions. High power microwave irradiation of a mixture of phenothiazine, alkyl halide and alcohol may afford satisfactory yields of N-alkyl-phenothiazines containing more than 2 carbon atoms in the side chain.

EXPERIMENTAL SECTION

Microwave installation *Synthos 3000* equipped with temperature and pressure sensors, power control and software operation.

Merck reagents.

400 MHz NMR spectrometer Bruker Avance

Microwave assisted synthesis of N-alkyl-phenothiazine, general procedure:

The reaction mixture (phenothiazine, alkylhalide, as well as any starting materials required according to conditions listed in table 1) solved in the properly chosen solvent was introduced in the quartz reaction vessel, which was sealed and then subjected to microwave irradiation in the resonance cavity of the microwave power system. Samples temperatures were automatically monitored during the irradiation with the prescribed power level. Inside pressure was monitored during the experiment. After irradiation, the solvent was removed by filtration and the solid product was purified by recrystallization.

10-methyl-10*H*-phenothiazine 1

a) 5 mmol (1g) phenothiazine, 6.4 mmol (0.4 ml) methyl iodide, 10 ml MeOH were treated according to the general procedure and the parameters listed in table 1 were applied.

b) *Microwave assisted PTC methylation*

A mixture of 1.25 mmol (1g) phenothiazine, 1.6 mmol (0.1 ml) methyl iodide, 5 ml BuOH, 5 ml of 10% KOH aq. and catalytic ammounts of Aliquat 336 was vigorously stirred in the closed vessel, while microwave irradiation was applied according to conditions described in table 1. The resulted reaction mixture was pourred in water and the product was extracted in dichloromethane After solvent removal, the crude product was recrystallised from EtOH.

Recristallyzation from EtOH. White crystals m.p.= 99,5°C, (lit. 99°C, 101-103 °C [14])

^{1}H-RMN 400MHz**,** $CDCl_3$: δ(ppm): 3,38ppm (s, 3H, H_a); 6,82ppm (d, 2H, $^3J_{orto}$= 8,4Hz, H_1); 6,93ppm (td, 2H, H_3); 7,14ppm (dd, 2H, $^3J_{orto}$= 7,1Hz, $^4J_{meta}$= 1,2Hz, H_4); 7,17ppm (td, 2H, $^4J_{meta}$= 1,2Hz, H_2) **^{13}C-RMN,** $CDCl_3$:δ(ppm): 35,3ppm (CH_3, C_a); 114,0ppm (CH, C_1); 122,4ppm (CH, C_3); δ=123,4ppm (Cq, C_{4a}); 127,1ppm (CH, C_2); 127,4ppm (CH, C_4); 145,80ppm (Cq, C_{9a}).

10-ethyl-10*H*-phenothiazine 2

1.25 mmol (0.25g) phenothiazine, 1.6 mmol (0.2 ml) ethyl iodide, 10 ml EtOH were treated according to the general procedure and the parameters listed in table 1 were applied.

Recristallyzation from EtOH. White crystals m.p.= 104.5°C (lit. 101-103°C [14])

^{1}H-RMN 400MHz , $CDCl_3$: δ(ppm): 1,38ppm (t, 3H, ^{3}J= 6,8Hz, H_b); 3,88ppm (q, 2H, ^{3}J= 6,8Hz, H_a); 6,83ppm (d, 2H, $^3J_{orto}$= 8,0Hz, H_1); 6,87ppm (t, 2H, H_3); 7,11ppm (m, 4H, $^3J_{orto}$= 7,6Hz, $H_{2,4}$) **^{13}C-RMN,** $CDCl_3$: δ(ppm): 13,0ppm (CH_3, C_b); 41,7ppm (CH_2, C_a); 115,0ppm (CH, C_1); 122,2ppm (CH, C_3); 124,4ppm (Cq, C_{4a}); 127,2ppm (CH, C_2); 127,3ppm (CH, C_4); 144.9ppm (CH, C_{9a})

10-isopropyl-10*H*-phenothiazine 3

1.25 mmol (0.25g) phenothiazine, 1.6 mmol (0.15 ml) *i*-propyl bromide, 10 ml *i*-PrOH were treated according to the general procedure and the parameters listed in table 1 were applied.

Recristallyzation from EtOH. m.p.= 60,5°C (lit 59-60 °C [14]

^{1}H-RMN 400MHz, $CDCl_3$: δ(ppm): 1,38ppm (d, 6H, ^{3}J= 7,2Hz, H_b); 3,46ppm (m, 2H, ^{3}J= 7,2Hz, H_a); 6,90ppm (t, 2H, H_3); 7,01ppm (d, 2H, $^3J_{orto}$= 8,2Hz, H_1); 7,17ppm (m, 4H, $^3J_{orto}$= 7,3Hz, $H_{2,4}$) **^{13}C-RMN, $CDCl_3$:** δ(ppm): 16,5ppm (CH_3, C_b); 33,7ppm (CH, C_a); 115,0pm (CH, C_1); 122,4ppm (CH, C_3); 123,4ppm (CH, C_{4a}); 127,2ppm (CH, C_2); 127,4ppm (CH, C_4); 145,1ppm (CH, C_{9a})

ACKNOWLEDGMENTS

Financial support from Roumanian Ministery of Education Research, Youth and Sports, grant PN-II-ID-564 is greatly acknowledged.

REFERENCES

1. T. Kline, E. Sieber-McMaster, W.F.Lau, S. Natarajan, *Bioorg. & Med. Chem. Lett.*, **1997**, *7(8),* 1017.
2. S. Ebdrup, *Synthesis*, **1998**, *8*, 1107.
3. T. J. J. Müller, *Tetrahedron Letters*, **1999**, *40*, 6563.
4. Ng. Ph. Buu-Hoï, N. G. Hoán, *J. Chem. Soc.*, **1951**, 1834.

5. G. Cauquil, E. Casadevall, R. Greze, *Bull. Soc. Chim. Fr.*, **1964**, 590.
6. V. Fărcăşan, *Rev. Roum. Chim.*, **1970**, *15*, 178.
7. A. Bernthsen, *Ann.*, **1885**, *230*, 88.
8. R. R. Gupta, *Phenothiazines and 1,4-benzothiazines Chemical and Biomedical aspects* in Bioactive Molecules, Elsevier, **1988**, chapter 1.
9. Ng. Ph. Buu-Hoï, N. G. Hoán, *J. Chem. Soc.*, **1951**, 1834.
10. C. Lespagnol, *Bull. Soc. Chim. Fr.*, **1959**, 112.
11. A. Loupy (Ed), *Microwaves in Organic Chemistry*, Wiley-VCH Weinheim, **2002.**
12 P. Lidstrom, J. P. Tierney *(*Eds), *Microwave-Assisted Organic Synthesis*, Blackwell, Oxford, **2004**.
13. P. T. Anastas, J. C. Warner, "*Green Chemistry Theory and Practice*", Oxford Univ. Press, **1998**.
14. S. P. Massie, *Chem. Rev.*, **1954**, *54*, 797.
15. H. Bernstein, L. Rothstein, *J. Am. Chem. Soc.*, **1944**, *66*, 1886.