# On the microwave-assisted synthesis of acylphenothiazine derivatives — Experiment versus theory synergism

**Luiza Gaina, Dan Porumb, Ioan Silaghi-Dumitrescu, Castelia Cristea, and Luminita Silaghi-Dumitrescu**

**Abstract:** The microwave-assisted synthesis of a series of acylphenothiazine derivatives is described. 10*H*-Phenothiazine-3-carbaldehyde derivatives were obtained in moderate yields by the Duff formylation reaction, and 10-acetyl-phenothiazine derivatives were obtained in excellent yields by acetylating phenothiazine derivatives with acetic anhydride. A theoretical explanation for the chemoselectivity and regioselectivity of these acylation reactions applied to phenothiazine substrates was attempted by molecular-modeling analyses based on molecular mechanics, and semi-empirical and DFT calculations.

*Key words:* phenothiazine, microwave-assisted organic synthesis (MAOS), Duff formylation, acetylation, DFT calculations, electrostatic potential.

**Résumé :** On décrit la synthèse assistée par des microondes d'une série de dérivés de l'acylphénothiazine. On a obtenu le 10*H*-phénothiazine-3-carbaldéhyde avec des rendements modérés en faisant appel à une réaction de formylation de Duff alors que les dérivés de la 10-acétylphénothiazine ont été obtenus avec d'excellents rendements par acétylation des dérivés de la phénothiazine à l'aide d'anhydride acétique. On a essayé de trouver une explication théorique de la chimiosélectivité et de la régiosélectivité de ces réactions d'acylation appliquées à des substrats phénothiazines en faisant appel à des analyses de modelages moléculaires basés sur des calculs de mécanique moléculaire, semi-empiriques ou des calculs basés sur la théorie de la théorie de la fonctionnelle de densité.

*Mots-clés :* phénothiazine, synthèses organiques assistées par des microondes (SOAM), formylation de Duff, acétylation, calculs basés sur la théorie de la théorie de la fonctionnelle de densité (TFD), potentiel électrostatique.

[Traduit par la Rédaction]

## Introduction

The increased popularity of the microwave-assisted organic synthesis (MAOS) technique in chemical synthesis on a laboratory scale is based on particularly efficient heating processes which afford shorter reaction times and offer the possibility of rapid optimization of the reaction conditions. An increasing number of published papers, several books,[1,2] and review articles show that almost all conventionally heated reactions, including synthesis and functionalization of heterocyclic compounds, were performed using this technique.[3,4,5] Since 1986, when Gedye[6] and Giguere[7] carried out the first reported organic syntheses using sealed vessels heated in domestic microwave ovens, several methods have been developed for the preparation of samples (with or without solvent) in both pressurized or open vessel systems; meanwhile dedicated multimode or monomode microwave reactors have been designed. Phenothiazine derivatives were obtained by microwave-assisted thiation of diarylamines in reactions of neat reactants or adsorbed onto inorganic supports such as alumina and bentonite,[8,9] and in water as a solvent.[10] Chalcones containing phenothyazine units were succesfully synthesized by microwave-assisted condensation of (hetero)aromatic carbonyl derivatives.[11]

One aim of this work was to optimize the microwave-assisted reaction conditions, as an eco-friendly approach for the synthesis of acyl-phenothiazine derivatives. These derivatives might prove to be useful substrates in the formation of coupled hetereocyclic systems, by forming new C=C bonds in condensation reactions. Suitable substituted phenothiazine derivatives are candidates for developing potentially interesting organic solid-state properties (such as unconventional physical, nonlinear optical, magnetic, and (or) electrical properties), based on the well-known electron donor effect of the phenothiazine nucleus characterized by low and highly reversible first oxidation potential and a pronounced tendency to form stable cation-radicals.[12] Furthermore, when the 10*H*-phenothiazine unit appears unsubstituted at the heterocyclic nitrogen atom, the cation-radical formed by single-electron oxidation may be involved in protolytic equilibria as well, thus generating the isoelectronic conjugate base, the neutral radical.[13–15] Potential new materials may be obtained using such redox-active and pH-sensitive heterocyclic building blocks.

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**L. Gaina, D. Porumb,[1] I. Silaghi-Dumitrescu, C. Cristea, and L. Silaghi-Dumitrescu.** Babeş-Bolyai University, Faculty of Chemistry and Chemical Engineering, 11, Arany Janos Street, 400028 Cluj-Napoca, Romania.

[1]Corresponding author (e-mail: pdan@chem.ubbcluj.ro).

## Experimental techniques

To ensure highly reproducible reaction conditions, the experimental technique employed for the microwave-assisted syntheses of acylphenothiazine derivatives described below is based on microwave power processing of materials using a microwave instrument Synthos 3000; this system provides multi-mode heating in sealed vessels equipped with built-in magnetic stirrer, pressure sensors, and internal temperature measurement. The instrument ensures cooling mechanisms, online power, and temperature control using the feedback from IR thermography. Software operation provides high-precision reaction control.

## Results and discussion

The chemical reactivity of phenothiazine towards electrophilic substitution was demonstrated in the preparation of numerous examples of N- or C-substituted derivatives. Chemical syntheses of acylphenothiazine derivatives were previously performed under conventional heating techniques which required long reaction times and usually generated mixtures of constitutional isomers. Although phenothiazine carbaldehydes were obtained by Vilsmeyer formylation[16] and Bergman formylation[17] of *N*-alkyl-phenothiazine derivatives, this method is inappropriate for the C-formylation of 10*H*-phenothiazine because of the formation of *N*-formyl-phenothiazine derivatives in competitive reactions. We wish to report here a direct and C-regioselective formylation of 10*H*-phenothiazine substrates, based on the Duff reaction,[18] as the only reaction strategy generating good yields of 10*H*-phenothiazin-3yl-carbaldehydes. Our promising results obtained by the microwave-assisted Duff formylation of unsubstituted 10*H*-phenothiazine[11] encouraged us to continue to apply this mild formylation reaction to several other substrates such as methyl-, halogeno-, and trifluoromethyl-10*H*-phenothiazine.

### Microwave-assisted synthesis of 10*H*-phenothiazine-3-carbaldehyde derivatives

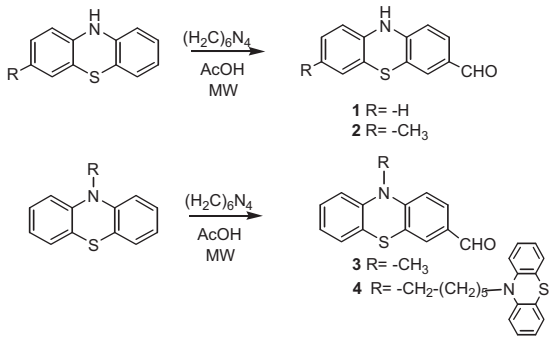
The microwave-assisted synthesis of 3-formyl-10*H*-phenothiazine derivatives was performed in the resonance cavity of a Synthos 3000 instrument by multimode microwave irradiation in pressurized systems (sealed quartz vessels) using acetic acid, a polar solvent which ensures a medium absorption efficiency and heating rate (tanδ = 0.174, dielectric loss $\varepsilon'' = 1.079$).[19]

3-Formyl-10*H*-phenothiazine (**1**) was synthesized in moderate yields by the microwave-assisted reaction of 10*H*-phenothiazine with urotropine in acetic acid solution. The same regioselectivity for substitution in position 3 of the heterocyclic substrate was observed in the microwave-assisted Duff formylation of some alkyl-substituted 10*H*-phenothiazine derivatives such as 3-methyl-phenothiazine, 10-methyl-phenothiazine, and 1,6-bis-(phenothiazin-10-yl)-hexane (Scheme 1).

The microwave-assisted Duff formylation reactions of some 2-substituted phenothiazine derivatives were also performed. As shown in Scheme 2, different carbaldehyde regioisomers may be formed according to the influence exerted by the substituent.

Electron-withdrawing substituents such as chlorine or trifluoromethyl group attached in position 2 of the phenothiazine substrate does not reduce the reactivity for electrophilic aromatic substitution in position 3, so that 3-formyl- and 7-formyl-phenothiazine derivatives were obtained. When 2-chlorophenothiazine was subjected to the Duff formylation reaction, the two monoformyl derivatives 2-chloro-7-formyl-phenothiazine (**5a**) and 2-chloro-3-formylphenothiazine (**5b**) were obtained in 1.5:1 ratio.

**Scheme 1.**




2-Trifluoromethyl-phenothiazine generated the 3,7-diformyl-2-trifluoromethylphenothiazine (**6**) as the main reaction product, in moderate yields.

The reaction conditions employed for these microwave-assisted syntheses (reaction temperature, reaction time, and ramp time to achieve the prescribed temperature) are shown in Table 1. Temperature-controlled experiments in the temperature range 150–190 °C show enhanced reactivity of unsubstituted phenothiazine as compared to substituted derivatives. Similar reaction conditions (time, temperature) were required for the formylation of alkyl-, 2-chloro-, and 2-trifluoromethyl-phenothiazine derivatives. Despite the alkyl chain length or its position in the substrate, mono formyl-derivatives were isolated, even in the case of 1,6-bis-(phenothiazin-10yl)-hexane which contains two equivalent phenothiazine units. Good yields of diformyl-phenothiazine derivative were obtained in the formylation of 2-trifluoromethyl-phenothiazine.

The regioselectivity of this reaction was experimentally proved by the failure of the formylation reaction when 3,7-dibromo-10-methylphenothiazine was subjected to a microwave-assisted Duff formylation reaction.

The structure assignments of compounds **1**–**6** are supported by spectroscopic data. FTIR spectroscopy indicates the stretching vibration of N–H bond in compounds **1**, **2**, **5**, and **6**, by the absorption band situated near 3300 $cm^{-1}$. The substitution in position 3 of the phenothiazine units was unambiguously assigned according to the NMR spectra. The coupling patterns of the aromatic protons observed for the $^1H$ NMR signals were assigned using the 2D homocorrelation COSY–45 spectra for each of products **1**–**6**. $^{13}C$ NMR spectra together with 2D NMR heterocorrelation spectra HMQC and HMBC afforded the complete structural assignments.

### Microwave-assisted synthesis of acetyl-10*H*-phenothiazine derivatives

Acetylation of 10*H*-phenothiazine derivatives using acetic anhydride generates different *N*-acetyl-10*H*-phenothiazine

**Scheme 2.**

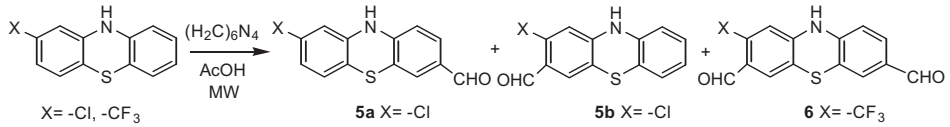
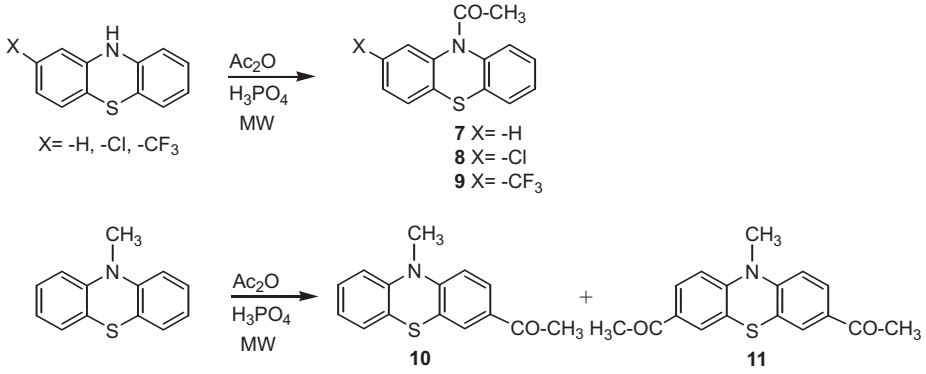



**Table 1.** Experimental conditions for the microwave-assisted Duff formylation reaction of phenothiazine derivatives using a Synthos 3000 microwave installation (reaction temperature, reaction time, and ramp time to achieve the prescribed temperature).

| Product | Substrate | *T* (°C) | Time/ramp (min) | Yield (%) |
|---|---|---|---|---|
| **1** | 10*H*-Phenothiazine | 120 | 30/10 | 50 |
| | | 150 | 80 | |
| | | 120 | 30 | |
| **2** | 3-Methyl-10*H*-phenothiazine | 150 | 5/4 | 50 |
| | | 170 | 60 | |
| | | 190 | 20 | |
| **3** | 10-Methyl-phenothiazine | 140 | 20/4 | 50 |
| | | 170 | 60 | |
| | | 180 | 10 | |
| **4** | 1,6-Bis-(phenothiazin-10yl)-hexane | 170 | 60/2 | 45 |
| | | 200 | 10 | |
| **5a** | 2-Chloro-10*H*-phenothiazine | 150 | 20/10 | 65 |
| **5b** | | 170 | 80 | **5a/5b** = 1.5:1 |
| **6** | 2-Trifluoromethyl-10*H*-phenothiazine | 150 | 5/4 | 65 |
| | | 170 | 99 | |
| | | 180 | 30 | |
| — | 3,7-Dibromo-10*H*-phenothiazine | 100 | 10/5 | — |
| | | 170 | 30 | |

**Scheme 3.**




and *C*-acetyl-10*H*-phenothiazine regioisomers according to the reaction conditions applied.[20,21]

The microwave-assisted acetylation of phenothiazine substrates was found to be highly chemoselective; *N*-acetyl-phenothiazine derivatives were obtained in almost quantitative yields. Scheme 3 presents the reactions of phenothiazine derivatives with acetic anhydride in the presence of catalytic amounts of phosphoric acid.

In the microwave-assisted acetylation of 10-methyl-phenothiazine, 3-acetyl-10-methylphenothiazine (**10**) was obtained in excellent yields. Table 2 summarizes the experimental conditions employed for the microwave-assisted acetylation of phenothiazine derivatives.

As expected, the less-reactive substrate in the acetylation reaction was *N*-methylphenothiazine. When longer reaction time was allowed, 3,7-diacetyl-10-methylphenothiazine (**11**) was obtained in good yields.

Spectroscopic data support the structure assignment of acetyl-derivatives **7**–**11**. The recorded 300 MHz $^1$H NMR spectra show the diagnostic appearance of a singlet signal for the acetyl group protons situated at 2.5 . Complete structural assignment for the aromatic protons and carbon atoms was performed by 2D NMR correlation spectra (COSY-45, HMQC and HMBC).

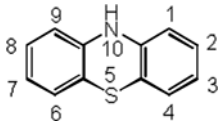
## Molecular modeling

The chemoselectivity and regioselectivity of these acylation reactions of the phenothiazine nucleus observed by experimental results were compared with theoretical data generated by DFT calculations.

**Table 2.** Experimental conditions for the microwave-assisted acetylation reaction of phenothiazine derivatives using a Synthos 3000 microwave installation (reaction temperature, reaction time, and ramp time to achieve the prescribed temperature).

| Product | Substrate | *T* (°C) | Time/ramp (min) | Yield (%) |
|---|---|---|---|---|
| **7** | 10*H*-Phenothiazine | 60 | 10/2 | 98 |
| | | 70 | 30 | |
| **8** | 2-Chloro-10*H*-phenothiazine | 60 | 10/2 | 96 |
| | | 70 | 30 | |
| **9** | 2-Trifluoromethyl-10*H*-phenothiazine | 60 | 10/2 | 97 |
| | | 70 | 30 | |
| **10** | 10-Methyl-phenothiazine | 60 | 5/3 | 45 |
| | | 80 | 10 | |
| **11** | 10-Methyl-phenothiazine | 60 | 5/3 | 55 |
| | | 80 | 30 | |

**Table 3.** Electrostatic atomic charges calculated in phenothiazine substrates and intermediates, candidates for aromatic electrophilic substitution.

|  | Electrostatic atomic charge in positions: | | | | |
|---|---|---|---|---|---|
| Compound | 2 | 3 | 7 | 8 | 10 |
| 10*H*-Phenothiazine | –0.038 | –0.226 | –0.226 | –0.038 | –0.661 |
| 10-Methylphenothiazine | –0.131 | –0.175 | –0.175 | –0.131 | –0.213 |
| 1,6-Bis(phenothiazin-10-yl)-hexane | –0.111 | –0.189 | –0.156 | –0.150 | –0.512 |
| 3-Methyl-10*H*-phenothiazine | –0.257 | 0.365 | –0.121 | –0.059 | –0.616 |
| 2-Chloro-10*H*-phenothiazine | 0.109 | –0.201 | –0.213 | –0.051 | –0.638 |
| 2-Trifluoromethyl-10*H*-phenothiazine | 0.175 | –0.299 | –0.193 | –0.055 | –0.629 |
| 2-Chloro-3-formyl-10*H*-phenothiazine | 0.173 | –0.027 | –0.236 | –0.031 | –0.618 |
| 2-Chloro-7-formyl-10*H*-phenothiazine | 0.234 | –0.297 | –0.013 | –0.044 | –0.607 |
| 3-formyl-2-trifluoromethyl-10*H*-phenothiazine | 0.005 | –0.097 | –0.183 | –0.056 | –0.596 |
| 7-Formyl-2-trifluoromethyl-10*H*-phenothiazine | 0.175 | –0.358 | 0.044 | –0.079 | –0.615 |

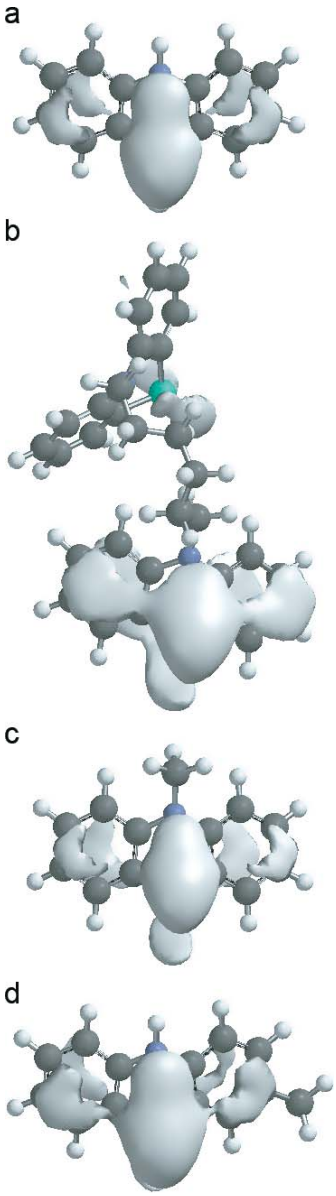
The minimum energy geometry of each phenothiazine derivative employed as a substrate in acylation reactions was obtained starting with molecular mechanics optimization of the conformers generated within the Confanal module of Spartan'06,[22] followed by semi-empirical (PM3) and 6–31G(d) B3LYP DFT[23–25] calculations on all such obtained conformers. The following discussion applies to the lowest energy conformers.

Theoretical explanations for the regioselectivity of the Duff formylation reaction and the chemoselectivity of the acetylation reaction, respectively, applied to substituted phenothiazine substrates may be formulated on the basis of the electrophilic aromatic substitution reaction mechanism. The soft electrophile $H_2C{=}N^+{<} \leftrightarrow H_2C^+{-}N{<}$ generated by urotropine during the Duff formylation reaction may selectively attack heterocyclic carbon atoms in positions characterized by high electron density, whereas the acylium ion $H_3C{-}CO^+$ generated by the acetic anhydride in acidic media is a hard electrophile and it is preferentially attached to the heterocyclic nitrogen atom. Here, we adopt the electrostatic charges derived from the electrostatic potential as an indicator of the preferred reaction site on the ring. These atomic charges given in Table 3 show the highest (negative) value on the nitrogen atom (position 10 of the heterocyclic substrate), followed by the values assigned to the carbon atoms in positions 3 and 7, for each phenothiazine substrate employed in experimental acylation reactions.

The electrostatic potential surfaces (–18 kcal/mol isovalues) for relevant alkylphenothiazine substrates are also shown in Fig. 1. In each case, it can be noticed that the region around position 3 of the substrate exhibits a relatively high area of negative electrostatic potential, thus supporting the availability of this atom to electrophilic attack, in agreement with experimental data regarding the regioselective aromatic electrophilic substitution performed by the soft electrophile (see Schemes 1 and 2). Notable is the shape of the –18 kcal/mol electrostatic potential surface for 1,6-bis(phenothiazin-10-yl)-hexane (Fig. 1b) located only on one of the phenothiazine rings suggesting that only one of the rings is subjected to a possible electrophilic attack. Indeed, experimental data show that only a monocarbaldehyde **4** is formed under the experimental conditions within this work.

The formation of a mixture of carbaldehydes **5a** and **5b** in a 1.5:1 ratio (Table 1) during the formylation of 2-chlorophenothiazine is understandable in view of the electrostatic charges (Table 3) in positions 7 (–0.213) and 3 (–0.201). The generated electrostatic potential surface (isovalue –15 kcal/mol) for 2-chloro-10*H*-phenothiazine is shown in Fig. 2b and may also suggest the slightly higher preference for the formation of **5a**. Moreover, once position 3 (or 7) is substituted, no significant negative electrostatic potential is noticed in position 7 or 3 (Fig. 2a or 2c). According to Figs. 2a and 2c further electrophilic attack is suppressed since no negative electrostatic potential in position 7 of **5a**

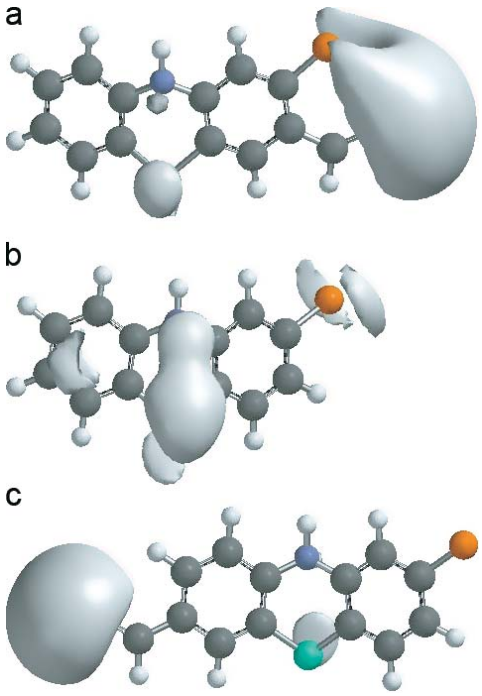
**Fig. 1.** Generated electrostatic potential (grayish envelope denotes negative electrostatic potential at isovalue –18 kcal/mol) for (a) 10*H*-phenothiazine, (b) 1,6-bis(phenothiazin-10-yl)-hexane, (c) 10-methylphenothiazine, (d) 3-methyl-10*H*-phenothiazine.




(Fig. 2a), or in position 3 of **5b** (Fig. 2c) is displayed. Thus, the formation of a 3,7-dicarbaldehyde derivative of 2-chloro-10*H*-phenothiazine is not expected and the experimental procedures applied to the formylation of 2-chlorophenothiazine confirmed the theoretical hypothesis by leading only to monocarbaldehydes **5a** and **5b**.

In contrast, the experimental formation of 3,7-dicarbaldehyde (**6**) is supported by possible formylation of 2-trifluoromethyl-10*H*-phenothiazine-monocarbaldehyde intermediates. Note in Fig. 3 that negative electrostatic potential surfaces appear around the carbon atoms in position 7 of the 3-carbaldehyde intermediate (Fig. 3c) and in position 3 of the 7-carbaldehyde intermediate, respectively (Fig. 3b).

**Fig. 2.** Generated electrostatic potential (grayish envelope denotes negative electrostatic potential at isovalue –15 kcal/mol); (a) 2-chloro-3-formyl-10*H*-phenothiazine (**5b**), (b) 2-chloro-10*H*-phenothiazine, (c) 2-chloro-7-formyl-10*H*-phenothiazine (**5a**).




## Conclusions

The Duff formylation reaction of phenothiazine derivatives appears for the moment as the only efficient alternative for obtaining new 10*H*-phenothiazine-3-carbaldehyde derivatives containing a free amino group able to participate in protolytic equilibria, as well as in redox processes characteristic for this heterocycle. The microwave-assisted Duff formylation reaction of phenothiazine derivatives is a technique which gives satisfactory experimental results affording good yields of 10*H*-phenothiazine-3-carbaldehyde derivatives.

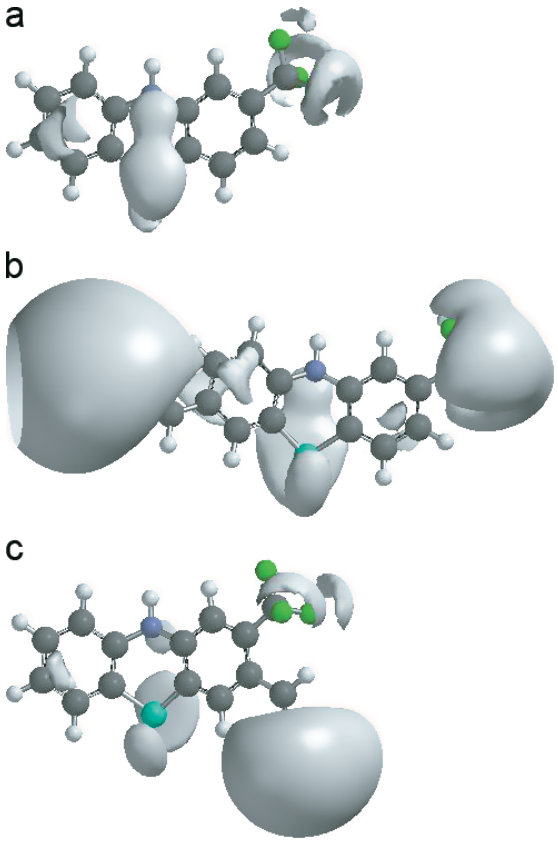
The microwave-assisted acetylation reaction produced good to almost quantitative yields, in most of the experiments performed using phenothiazine substrates. Comparison of microwave-assisted synthesis with the conventional synthetic methods demonstrates advantages related to shorter reaction times and higher regioselectivity.

The electrostatic potential surfaces generated on the basis of 6–31G(d) B3LYP calculations support the preference for electophilic attack and explain the regioselectivity of formylation reactions.

## Experimental section

The reactions were performed using a microwave installation Synthos 3000. Reagents from Merck were used. TLC was used to monitor the reaction progress (Merck silica gel F 254 plates). NMR spectra were recorded using a 300 MHz Brucker Avance NMR spectrometer. FTIR spectra were recorded using a Brucker Vector 22 FTIR spectrometer. Elemental analysis was carried out on a Thermo FlashEA 1112 Series instrument. The lowest-energy conformers generated

**Fig. 3.** The electrostatic potential surface (grayish envelope denotes negative electrostatic potential at isovalue –10 kcal/mol); (a) 2-trifluoromethyl-10*H*-phenothiazine, (b) 7-formyl-2-trifluoromethyl-10*H*-phenothiazine, (c) 3-formyl-2-trifluoromethyl-10*H*-phenothiazine.




by using the MMFF force field implemented in Spartan'04 have been further fully optimized using the 6–31G(d) B3LYP hybrid DFT method.[23–25]

## General procedure for microwave-assisted Duff formylation reaction of phenothiazine derivatives

The reaction mixture (5 mmol phenothiazine derivative and 7.5 mmol urotropine) dissolved in 20 mL acetic acid was introduced into the quartz reaction vessel, which was then sealed and subjected to microwave irradiation in the resonance cavity of the microwave power system. Prescribed sample temperatures were automatically monitored during the irradiation (Table 1). TLC was used to monitor the reaction progress. After irradiation, the reaction mixture was poured into water and neutralized with $Na_2CO_3$. Organic products were extracted in dichloromethane (3 × 20 mL). The combined organic layers were dried on anhydrous $Na_2SO_4$ and concentrated to dryness. The product was purified by column chromatography (silica gel, toluene).

### *10*H*-Phenothiazine-3-carbaldehyde (1)*

Yellow precipitate recrystallized from toluene, mp 192 °C.[11,26] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 9.24 (s, 1H, NH), 9.64 (s, 1H, CHO), 7.50 (dd, $^4J$ = 1.2 Hz, $^3J$ = 7.6 Hz, 1H, $H_2$), 7.35 (s, 1H, $H_4$), 7.00 (t, $^3J$ = 7.6 Hz, $^3J$ = 8 Hz, 1H, $H_8$), δ7.90 (d, $^3J$ = 8 Hz, 1H, $H_6$), 6.80(t, $^3J$ = 8 Hz, $^3J$ = 7.6, 1H, $H_7$), 6.70 (d, $^3J$ = 7.6 Hz, 1H, $H_1$), 6.75 (dd, $^3J$ = 8 Hz, $^4J$ = 2 Hz,1H, $H_9$). $^{13}$C NMR (75.4MHz,$CDCl_3$, ppm) δ: 113.88 (CH, $C_1$), 113.93 (CH, $C_9$), 116.69 ($C_{quat}$, $C_{4a}$), 115.77 ($C_{quat}$, $C_{5a}$), 130.43 (CH, $C_2$), 127.36 (CH, $C_4$), 123.07 (CH, $C_7$), 126.24 (CH, $C_6$), 127.83 (CH, $C_8$), 130.9 ($C_{quat}$, $C_3$), 139.57 ($C_{quat}$, $C_{9a}$), 147.12 ($C_{quat}$, $C_{10a}$). Anal. calcd. for $C_{13}H_9NOS$ (227.2): C 68.70, H 3.99, N 6.16; found: C 68.62, H 3.99, N 6.09.

### *7-Methyl-10*H*-phenothiazine-3-carbaldehyde (2)*

$^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.22 (s, 3H), 6.54 (d, $^3J$ = 7.5 Hz, 1H, $H_1$), 7.48 (d, $^3J$ = 7.5 Hz 1H, $H_2$), 7.44 (s, 1H, $H_4$), 6.78 (s, 1H, $H_6$), 9.72 (s, 1H, CHO), 6.81 (d, $^3J$ = 7.7 Hz, 1H, $H_8$), 6.44 (d, $^3J$ = 7.7 Hz, 1H, $H_9$), 6.04 (s, 1H, NH). Anal. calcd. for $C_{14}H_{11}NOS$ (241.3): C 69.68, H 4.59, N 5.80; found: C 69.60, H 4.58, N 5.85.

### *10-Methyl-10*H*-phenothiazine-3-carbaldehyde (3)*

Yellow precipitate recrystallized from toluene, mp 88 °C.[16,27] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 9.80 (s, 1H CHO), 7.65 (dd, $^4J$ = 2 Hz, $^3J$ = 8.4 Hz, 1H $H_2$), 7.59 (d, $^4J$ = 2 Hz, 1H, $H_4$), 7.18 (td, $^4J$ = 1.4 Hz, $^3J$ = 8.4 Hz, 1H, $H_8$), 7.12 (dd, $^4J$ = 1.4 Hz, $^3J$ = 7.6 Hz, 1H, $H_6$), 6.98 (t, $^3J$ = 7.6 Hz, $^3J$ = 8.4, 1H, $H_7$), 6.85 (d, $^3J$ = 8.4 Hz, 1H, $H_1$), 6.84 (d, $^3J$ = 8 Hz, 1H, $H_9$), 3.42 (s, 3H). $^{13}$C NMR (75.4 MHz, $CDCl_3$, ppm) δ: 35.84 ($CH_3$), 113.72 (CH, $C_1$), 114.78 (CH, $C_9$), 131.16 (CH, $C_3$), 123.98 ($C_{quat}$, $C_{4a}$), 122.53($C_{quat}$, $C_{5a}$), 130.48 (CH, $C_2$), 127.96 (CH, $C_4$), 123.64 (CH, $C_7$), 127.31 (CH, $C_6$), 127.78 (CH, $C_8$), 144.09 ($C_{quat}$, $C_{9a}$), 151.10 ($C_{quat}$, $C_{10a}$). Anal. calcd. for $C_{14}H_{11}NOS$ (241.3): C 69.68, H 4.59, N 5.80; found: C 69.59, H 4.58, N 5.87.

### *10-(6-(10*H*-Phenothiazin-10-yl)hexyl)-10H-phenothiazine-3-carbaldehyde (4)*

Yellow precipitate recrystallized from toluene, mp 98 °C.[28] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 3.85 (t, 4H), 1.79 (m, 4H), 1.46 (m, 4H), 9.80 (s, 1H), 6.86 (m, 4H, $H_{1,9}$), 6.92 (td, 2H, $H_{7'}$), 6.97 (td, 1H, $H_7$), 7.11 (dd, 1H, $H_6$), 7.15 (m, 5H, $H_{6',8,8'}$), 7.58 (dd, 1H, $H_4$), 7.62 (dd, 1H, $H_2$). $^{13}$C NMR (75.4 MHz, $CDCl_3$) δ: 26.73 ($CH_2$), 26.77 ($CH_2$), 26.99 ($CH_2$), 27.07 ($CH_2$), 47.41 ($CH_2$), 48.10 ($CH_2$), 115.29 (CH, $C_1$), 115.90 (2CH, $C_{1',9'}$), 116.44 (CH, $C_9$), 122.83 (2$C_{quat}$, $C_{4a'}$), 124.01 ($C_{quat}$, $C_{5a}$), 124.38 (CH, $C_7$), 125.60 ($C_{quat}$, $C_{4a}$), 127.60 (2CH, $C_{2',8'}$), 127.91 (2CH, $C_{4',6'}$), 127.98 (CH, $C_6$), 128.00 (CH, $C_4$), 128.82 (CH, $C_8$), 130.0 (CH, $C_2$), 131.50 (CH, $C_3$), 143.84 (2$C_{quat}$, $C_{9a'}$), 145.70 ($C_{quat}$, $C_{9a}$), 151.14 ($C_{quat}$, $C_{10a}$), 190.40 (CH, CHO). Anal. calcd. for $C_{31}H_{28}N_2OS_2$ (508.6) C 73.20, H 5.55, N 5.51, found: C 73.18, H 5.55, N 5.61.

### *8-Chloro-10*H*-phenothiazine-3-carbaldehyde (5a)*

Yellow precipitate recrystallized from toluene, mp 195 °C. $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 9.65 (s, 1H, CHO), 7.51 (dd, $^3J$ = 8.4 Hz $^4$, $J$ = 1.6 Hz, 1H, $H_2$), 7.37 (d, $^4J$ = 1.6 Hz, 1H, $H_4$), 6.92 (d, $^3J$ = 8.4 Hz, 1H, $H_6$), 6.84 (dd, $^3J$ = 8.4 Hz $^4$, $J$ =2 Hz, 1H, $H_7$), 6.73 (d, $^3J$ = 8.4 Hz, 1H, $H_1$), 6.71 (d, $^4J$ = 2 Hz, 1H, $H_9$). $^{13}$C NMR (75.4 MHz, $CDCl_3$, ppm) δ: 114.59 (CH, $C_1$), 114.49 (CH, $C_9$), 122.76 (CH, $C_7$), 127.63 (CH, $C_6$), 124.74 (CH, $C_2$), 130.78 (CH, $C_4$), 190.39 (CH, CHO), 115.19 ($C_{quat}$, $C_{5a}$), 116.82 ($C_{quat}$, $C_{5a}$), 132.28 ($C_{quat}$, $C_8$), 131.15 ($C_{quat}$, $C_3$),

141.24 ($C_{quat}$, $C_{9a}$), 146.35 ($C_{quat}$, $C_{10a}$). Anal. calcd. for $C_{13}H_8ClNOS$ (261.7): C 59.66, H 3.08, N 5.35; found: C 59.59, H 3.08, N 5.38.

***2-Chloro-10H-phenothiazine-3-carbaldehyde (5b)***

Brown precipitate recrystallized from toluene, mp 224 °C. $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 9.42 (s, 1H, NH), 9.96 (s, 1H, CHO), 7.27 (s, 1H, $H_4$), 7.01 (t, $^3J$ = 7.2 Hz, $^3J$ = 8 Hz, 1H, $H_8$), 6.91 (d, $^3J$ = 7.6 Hz, 1H, $H_6$), 6.83 (t, $^3J$ = 7.6 Hz, $^3J$ = 7.2 Hz, 1H, $H_7$), 6.66 (m, 2H, $H_{1,9}$). $^{13}$C NMR (75.4 MHz, $CDCl_3$, ppm) δ: 113.64 (CH, $C_9$), 115.09 ($C_{quat}$, $C_{5a}$), 115.93 (CH, $C_1$), 115.26 ($C_{quat}$, $C_{4a}$), 123.29 (CH, $C_7$), 125.18 (CH, $C_6$), 126.03 (CH, $C_8$), 126.28 (CH, $C_4$), 127.69 ($C_{quat}$, $C_3$), 136.35 ($C_{quat}$, $C_2$), 138.01 ($C_{quat}$, $C_{9a}$), 147.16 ($C_{quat}$, $C_{10a}$), 186.27 (CH, CHO). Anal. calcd. for $C_{13}H_8ClNOS$ (261.7): C 59.66, H 3.08, N 5.35; found: C 59.59, H 3.08, N 5.38.

***2-(Trifluoromethyl)-10H-phenothiazine-3,7-dicarbaldehyde (6)***

$^1$H NMR (300MHz, $CDCl_3$, ppm) δ: 9.42 (s, 1H, NH), 9.96 (s, 1H, CHO), 10.35 (s, 1H, CHO), 7.39 (s, 1H, $H_4$), 7.54 (dd, $^3J$ = 7.2 Hz, $^4J$ = 1.2 Hz 1H, $H_8$), 7.46 (d, $^2J$ = 1.2 Hz, 1H, $H_6$), 7.06 (s, 1H, $H_1$), 7,39 (d, $^3J$ = 7.2 Hz, 1H, $H_9$). $^{13}$C NMR (75.4 MHz, $CDCl_3$, ppm) δ: 115.95 (CH, $C_1$), 120.64 (CH, $C_9$), 118.09 ($C_{quat}$, $C_{5a}$), 122.26 ($C_{quat}$, $C_{4a}$), 131.29 ($C_{quat}$, $C_7$), 130.18 (CH, $C_6$), 129.03 (CH, $C_8$), 131.28 (CH, $C_4$), 121.69 ($C_{quat}$, $C_3$), 128.35 ($C_{quat}$, $C_2$), 148.01 ($C_{quat}$, $C_{9a}$), 148.16 ($C_{quat}$, $C_{10a}$), 190.27 (CH, CHO), 191.34 (CH, CHO). Anal. calcd. for $C_{15}H_8F_3NO_2S$ (323.2): C 55.73, H 2.49, N 4.33; found: C 55.69, H 2.49, N 4.42.

**General procedure for microwave-assisted acetylation reaction of phenothiazine derivatives**

The reaction mixture (phenothiazine derivative – acetic anhydride ratio 1:10 and phosphoric acid in catalytic amounts) was introduced into the quartz reaction vessel, which was then sealed and subjected to microwave irradiation in the resonance cavity of the microwave power system. Prescribed sample temperatures were automatically monitored during the irradiation (Table 2). TLC was used to monitor the reaction progress. After irradiation, the reaction mixture was poured on ice and neutralized. The precipitate formed was filtered and thoroughly washed with water. The product was purified by recrystallization in toluene.

***1-(10H-Phenothiazine-10-yl)ethanone (10-acetyl-10Hphenothiazine) (7)***

White crystals recrystallized from toluene, mp 199 °C.[29] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.13 (s, 3H, $CH_3$), 7.62 (d, $^3J$ = 8 Hz, 2H, $H_{1,9}$), 7.40 (t, $^3J$ = 8 Hz, 2H, $H_{2,8}$), 7.31 (t, $^3J$ = 7.2 Hz, $^3J$ = 7.6 Hz, 2H, $H_{3,7}$), 7.56 (d, $^3J$ = 7.6 Hz, 2H, $H_{4,6}$). $^{13}$C NMR ($CDCl_3$, ppm) δ: 127.93 (CH, $C_1$), 126.95 (CH, $C_2$), 126.67 (CH, $C_3$), 127.17 ($C_{quat}$, C5a), 22.39 ($CH_3$), 169.27 ($C_{quat}$, CO), 138.94 ($C_{quat}$, C10a). Anal. calcd. for $C_{14}H_{11}NOS$ (241.3): C 69.68, H 4.59, N 5.80; found: C 69.56, H 4.59, N 5.85.

***1-(2-Chloro-10H-phenothiazine-10-yl)ethanone (10-acetyl-2-chloro-10Hphenothiazine) (8)***

White precipitate recrystallized from toluene, mp 104 °C.[30] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.13 (s, 3H, $CH_3$), 7.47 (d, 1H, $H_1$, $^4J$ = 1.6 Hz), 7.36 (t, 1H, $H_8$, $^3J$ = 7.6 Hz), 7.35 (dd, 1H, $H_4$, $^3J$ = 7.6 Hz), 7.26 (m, 2H, $H_{3,6}$), 7.17 (td, 1H, $H_7$, $^4J$ = 1.6 Hz, $^3J$ = 7.6 Hz), 7.13 (dd, 1H, $H_9$, $^4J$ = 2 Hz, $^3J$ = 8.4 Hz). $^{13}$C NMR ($CDCl_3$, ppm) δ: 22.98 ($CH_3$), 169.07 (C=O), 132.57 (CH,$C_2$), 139.87 ($C_{quat}$, $C_{10a}$), 138.60 ($C_{quat}$, $C_{9a}$), 127.54 ($C_{quat}$), 127.09 (2CH), 128.45 (CH), 128.06 (CH), 127.27 (CH, C), 127.96 (CH, C). Anal. calcd. for $C_{14}H_{10}ClNOS$ (275.7): C 69.98, H 3.66, N 5.08; found: C 69.89, H 3.66, N 5.19.

***1-(2-(Trifluoromethyl)-10H-phenothiazine-10-yl)ethanone (9)***

$^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.21 (s, 3H, $CH_3$), 7.81 (s, 1H, $H_1$), 7,25 (td, 1H, $H_7$, $^3J$ = 7.6 Hz, $^3J$ = 7.7 Hz, $^4J$ = 1.6 Hz), 7.34 (td, 1H, $H_8$, $^3J$ = 8 Hz, $^3J$ = 7.7 Hz, $^4J$ = 1.6 Hz), 7.51 (d, 1H, $H_4$, $^3J$ = 8.4 Hz), 7.46 (m, 2H, $H_{4,9}$). $^{13}$C NMR ($CDCl_3$, ppm) δ: 22.88 ($CH_3$), 169.13 (C=O), 129.49 (CH, $C_2$), 123.45 ($C_{quat}$, $CF_3$), 124.46 ($C_{quat}$), 125.10 ($C_{quat}$), 139.05 ($C_{quat}$, $C_{10a}$), 138.42 ($C_{quat}$, $C_{9a}$), 127.09 (CH), 127.31 (2 CH), 127.57 (2 CH), 128.12 (CH), 128.17 (CH). Anal. calcd. for $C_{15}H_{10}F_3NOS$ (309.3): C 58.25, H 3.26, N 4.53, found: C 58.14, H 3.26, N 4.61.

***1-(10-Methyl-10H-phenothiazine-3yl)ethanone (10)***

Recrystallized from toluene, mp 101 °C.[21] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.51 (s, 3H, $CH_3$), 3.39 (s, 3H, $H_3C$), 6.7 (d, 1H, $H_1$), 7.76 (d, $^3J$ = 8.4 Hz, 1H, $H_2$), 7.69 (s, 1H, $H_4$), 7.12 (d, $^3J$ = 6.7 Hz, 1H, $H_6$), 6.97 (t, $^3J$ = 7.2 Hz, $^3J$ = 7.6, 1H, $H_7$), 7.17 (t, $^3J$ = 7.6 Hz, 1H, $H_8$), 6.82 (d, $^3J$ = 7.6 Hz, 1H, $H_9$). $^{13}$C NMR ($CDCl_3$, ppm) δ: 35.62 ($CH_3$), 26.22 ($CH_3$), 113.31 (CH, $C_1$), 128.77 (CH, $C_2$), 131.58 (CH, $C_3$), 123.19 ($C_{quat}$, $C_{4a}$), 122.63 ($C_{quat}$, $C_{5a}$), 127.23 (CH, $C_6$), 123.33 (CH, $C_7$), 127.30 (CH, $C_8$), 114.53 (CH, $C_9$), 127.66 (CH, $C_4$), 144.46($C_{quat}$, $C_{9a}$), 149.85 ($C_{quat}$, $C_{10a}$). Anal. calcd. for $C_{15}H_{13}NOS$ (255.3): C 70.56, H 5.13, N 5.49; found: C 70.46, H 5.13, N 5.55.

***1,1′-(10-Methyl-10H-phenothiazine-3,7-diyl)diethanone (11)***

Yellow-green precipitate recrystallized from toluene (64 % yield), mp 202 °C.[31] $^1$H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.54 (s, 6H, $CH_3$), 3.46 (s, 3H, $CH_3$), 6.84 (d, $^2J$ = 10 Hz, 2H, $H_{1,9}$), 7.70 (s, 2H, $H_{4,6}$), 7.79 (d, $^2J$ = 10 Hz, 2H, $H_{2,8}$). $^{13}$C NMR ($CDCl_3$, ppm) δ: 26.7 ($CH_3$), 36.4 ($CH_3$), 114.4 (CH, $C_{1,9}$), 123.3 ($C_{quat}$, $C_{4a}$), 127.8 (CH, $C_{4,6}$), 129.1 (CH, $C_{2,8}$), 132.9 ($C_{quat}$, $C_{3,7}$), 148.9 ($C_{quat}$, $C_{9a}$), 196.4 ($C_{quat}$, CO). Anal. calcd. for $C_{17}H_{15}NO_2S$ (297.3): C 68.66, H 5.08, N 4.71; found: C 68.59, H 5.08, N 4.78.

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