Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
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A new synthetic approach and biological evaluation of novel phenothiazines bearing tert-butyl group

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First Published on: 18 August 2009

To cite this Article Trivedi, Amit R., Siddiqui, Arif B., Dodiya, Dipti K., Soalnki, Manish J. and Shah, Viresh H.(2009)'A new synthetic approach and biological evaluation of novel phenothiazines bearing tert-butyl group',Journal of Sulfur Chemistry,99999:1,

To link to this Article: DOI: 10.1080/17415990903173511

URL: http://dx.doi.org/10.1080/17415990903173511

Journal of Sulfur Chemistry
iFirst, 2009, 1–7

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A new synthetic approach and biological evaluation of novel phenothiazines bearing *tert*-butyl group

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(*Received 16 October 2007; final version received 27 June 2009*)

A new and facile synthetic route is proposed for the synthesis of some novel phenothiazines (**5a**–**5g**) based on the reaction of 2-amino substituted benzenethiols with *p-tert*-butyl phenol in good yield. The newly synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral studies. Their antimicrobial activities against three strains of bacteria: *Bacillus subtilis*, *Bacillus megaterium*, *Escherichia coli*, and two strains of fungi: *Aspergillus niger* and *Aspergillus oryzae*, were investigated.

Keywords: phenothiazine; *p-tert*-butyl phenol; 2-amino benzenethiols; oxidative cyclization; antimicrobial activity

1. Introduction

During the past five decades, studies devoted to the phenothiazine class of compounds (*1–4*) have been stimulated by the discovery of the pharmacodynamic properties of a number of derivatives in which a variety of amino alkyl side chains are connected to the nitrogen atom of the heterocyclic unit. Consequently, drugs incorporating a phenothiazine ring system (*5–7*) have played a crucial role in medicinal chemistry and have occupied a place of choice in the arsenal of pharmaceutical drugs, owing to their antimicrobial (*8*), tranquilizing (*9*), anti-inflammatory (*10*), antimalarial (*11*), antipsychotropic (*12*), antitubercular (*13*, *14*) and antitumor (*15–17*) properties, and for their ability to stimulate the penetration of anticancer agents via blood-brain barrier.

A slight variation in the substitution pattern in the phenothiazine nucleus causes a marked difference in activity, and therefore phenothiazines with varied substituents are being synthesized and tested for activities in search of better medicinal agents. Moreover, in spite of its very simple hydrocarbon structure, the *tert*-butyl group has attracted much attention from organic chemists for many decades due to its unique biomedical applications and significant contribution in the enhancement of bioactivities (*18–24*). Keeping in mind the biomedical applications, as a continuation of our previous work (*25*) and with a view to further assess the pharmacological profile of this class of compounds, we thought it worthwhile to synthesize some new congeners of phenothiazines **5a**–**5g** by incorporating the phenothiazine nucleus and *tert*-butyl group in a single

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ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415990903173511
http://www.informaworld.com

molecular framework with a potential spectrum of bio-responses. The antimicrobial activities of the newly synthesized compounds **5a**–**5g** against three strains of bacteria: *Bacillus subtilis*, *Bacillus megaterium* and *Escherichia coli*, and two strains of fungi: *Aspergillus niger* and *Aspergillus oryzae*, were investigated.

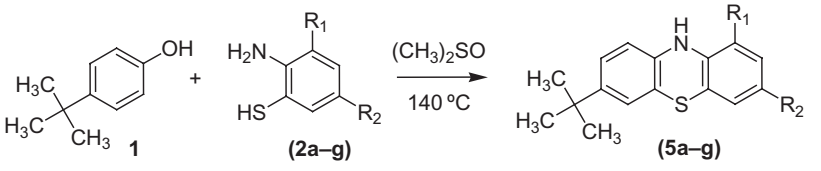
2. Chemistry

To the best of our knowledge, there are no previous reports in the literature for phenothiazines having a *tert*-butyl group. A literature survey reveals general synthetic strategies towards phenothiazines, such as thionation of diphenylamines (*26*), reaction of aminothiols with halonitro or dihalogenobenzene derivatives (*27*), cyclization of diphenyl sulfides (*28*), condensation of aminothiols with quinone or 1,3-dione (*29*), cyclization of 2-substituted diphenylamines (*30*), etc., which require long reaction times or include multi-step synthesis. In contrast, for the same reaction performed under our conditions, the reaction time was markedly reduced and improvement in yields was also observed. The work up is simple and does not require any tedious procedures.

Herein we report a novel, efficient, single-step synthesis of novel phenothiazines bearing a *tert*-butyl group (**5a**–**5g**). The synthetic pathway for the preparation of the title compounds **5a**–**5g** is depicted in Scheme 1.

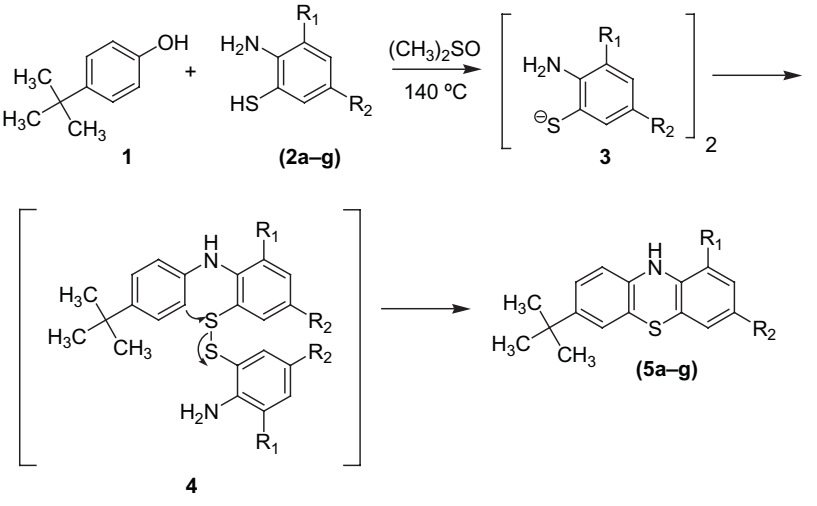
The ring system **5a**–**5g** was obtained *via* oxidative cyclization (*31*) by merely heating a mixture of *p-tert*-butyl phenol (**1**) and appropriately substituted 2-mercapto aniline (**2a**–**5g**) in dimethyl sulfoxide at 140 °C for 45 min. Since the 2-mercapto anilines (**2a–g**) readily oxidize to bis (*o*-aminophenyl)disulfide (**3**) under these reaction conditions, the reaction is considered to proceed via the intermediate **4**, which is readily cyclized by the scission of the sulfur–sulfur bond (*32*, *33*) upon the attack by the nucleophilic enaminone system. The possible mechanism of the reaction is proposed in Scheme 2.

The IR spectra of **5a**–**5g** exhibit a sharp peak in the region 3300–3350 cm^{-1} due to −NH stretching vibrations, and a sharp peak in the range of 600–700 cm^{-1}, suggesting the presence of C−S−C linkage. Phenothiazines **5d** and **5g** having a chlorine atom show a peak in the range of 720–780 cm^{-1}. In phenothiazines **2c** and **2f**, two peaks appear in the range of 1050–1075 cm^{-1} and 1200–1275 cm^{-1} due to asymmetric and symmetric vibrations of C−O−C linkage. The ^{1}H NMR spectra of phenothiazines **5a**–**5g** exhibit a broad signal in the region 9.01–9.92 δ due to an NH proton, while aromatic protons appear as a multiplet between 7.11–8.91 δ. In all phenothiazines **5a**–**5g**, a sharp singlet of 9H was observed in the range of 1.28–1.45 δ due to the presence of a *tert*-butyl group.



	R1	R2
2a, 5a	H	H
2b, 5b	CH3	H
2c, 5c	OCH3	H
2d, 5d	Cl	H
2e, 5e	H	CH3
2f, 5f	H	OCH3
2g, 5g	H	Cl

Scheme 1.



Scheme 2.

3. Biological activity

Compounds **5a**–**5g** were screened *in vitro* for their antimicrobial activities against three strains of bacteria: *B. subtilis*, *B. megaterium*, *E. coli*, and two strains of fungi: *A. niger* and *A. oryzae*, by the agar-diffusion technique (*34*). A 1 mg/ml solution in dimethylformamide was used. The bacteria and fungi were maintained on nutrient agar and Czapek's-Dox agar media, respectively. DMF showed no inhibition zones. The agar media were incubated with different microorganism cultures. After 24 h of incubation at 30 °C for bacteria and 48 h of incubation at 28 °C for fungi, the diameter of the inhibition zone (mm) was measured (Table 1). Ampicillin, chloramphenicol and fluconazole were purchased from an Indian market and used in a concentrations of 25 mg/ml as references for antibacterial and antifungal activities. The results depicted in Table 1 revealed that phenothiazines **5a**, **5b**, **5e**, **5g** and **5h** showed a very high activity with respect to the used references, while phenothiazines **5c** and **5f** showed comparable activity. On the other hand, nearly all

Table 1. Inhibition zone (mean diameter of inhibition, in mm) as a criterion of antibacterial and antifungal activities of the newly synthesized phenothiazine derivatives.

	Inhibition zone				
	Gram-positive bacteria		Gram-negative bacteria	Fungi	
	B. subtilis	*B. megaterium*	*E. coli*	*A. niger*	*A. oryzae*
Compound					
5a	69	56	56	69	68
5b	41	46	59	56	72
5c	36	42	29	62	65
5d	53	61	69	53	69
5e	44	57	57	71	77
5f	32	35	26	72	63
5g	60	69	55	63	76
Reference drugs					
Ampicillin	40	29	26	33	–
Chloramphenicol	30	55	48	35	–
Fluconazole	–	–	–	22	16

of the prepared compounds exhibited an interesting high antifungal activity against the reference chemotherapeutics.

4. Conclusion

To sum up, we have developed a concise and efficient approach for the synthesis of some novel phenothiazines bearing a *tert*-butyl group. We also believe that the procedural simplicity, efficiency and the easy accessibility of the reaction partners should be rewarded by giving access to a wide array of heterocyclic frameworks equipped with a pendant phenothiazine unit. Further work is under progress to design new synthetic methodologies for phenothiazines, and for screening these compounds for their biological activities.

5. Experimental

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5-mm thickness, and spots were located by iodine. ^{1}H NMR spectra were determined in a $CDCl_3$ solution at 300 MHz on a Bruker spectrometer. IR spectra were recorded using a Shimadzu 8400 spectrometer in KBr (γ in cm^{-1}). Elemental analysis of the newly synthesized compounds was carried out on a Carlo Erba 1108 analyzer.

5.1. *General experimental procedure*

A mixture of *p-tert*-butyl phenol **1** (0.01 mol), respective 2-mercapto aniline **2a**–**2g** (0.01 mol) in dimethyl sulfoxide (10 ml) was heated with stirring at 140–145 °C form 45 min. The crystalline product **5a**–**5g** separated on cooling was filtered and recrystallized from methanol.

5.2. *7-Tert-butyl-10H-phenothiazine (5a)*

Yield 78%, m.p. 177 °C; IR (KBr) cm^{-1}: 3334 (NH), 1328 (C−N), 653 (C−S−C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (s, 9H, *tert*-Bu), 7.21–8.40 (m, 7H, Ar−H), 9.11 (s, 1H, NH); MS: m/z 255; Anal. calcd. for $C_{16}H_{17}NS$: C, 75.25; H, 6.71; N 5.48. Found: C, 75.29; H, 6.73; N, 5.54%.

5.3. *7-Tert-butyl-1-methyl-10H-phenothiazine (5b)*

Yield 83%, m.p. 204 °C; IR (KBr) cm^{-1}: 3335 (NH), 1332 (C−N), 655 (C−S−C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 (s, 9H, *tert*-butyl), 2.46 (s, 3H, CH_3), 7.43–8.21 (m,6H, Ar−H), 9.01 (s, 1H, NH); MS: m/z 269; Anal. calcd. for $C_{17}H_{19}NS$: C, 75.79; H, 7.11; N, 5.20. Found: C, 75.83; H, 7.16; N, 5.25%.

5.4. *7-Tert-butyl-1-methoxy-10H-phenothiazine (5c)*

Yield 74%, m.p. 118 °C; IR (KBr) cm^{-1}: 3338 (NH), 1330 (C−N), 650 (C−S−C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 9H, *tert*-butyl), 3.67 (s, 3H, OCH_3), 7.80–8.91 (m, 6H, Ar−H), 9.73 (s, 1H, NH); MS: m/z 285; Anal. calcd. for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.5; H, 6.77; N, 4.88%.

5.5. *7-Tert-butyl-1-chloro-10H-phenothiazine (5d)*

Yield 85%, m.p. 167 °C; IR (KBr) cm^{-1}: 3332 (NH), 1325 (C−N), 648 (C−S−C); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.38 (s, 9H, *tert*-butyl), 7.11–8.36 (m, 6H, Ar−H), 9.28 (s, 1H, NH); Mass (m/z): 290; Anal. calcd. for $C_{16}H_{16}N_5SCl$: C, 66.31; H, 5.56; N, 4.83. Found: C, 66.36; H, 5.53; N, 4.88%.

5.6. *3-Tert-butyl-7-methyl-10H-phenothiazine (5e)*

Yield 82%, m.p. 137 °C; IR (KBr) cm^{-1}: 3337 (NH), 1327 (C−N), 645 (C−S−C); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 9H, *tert*-butyl), 2.52 (s, 3H, CH_3), 7.37–8.44 (m, 6H, Ar−H), 9.18 (s, 1H, NH); MS: m/z 269; Anal. calcd. for $C_{17}H_{19}NS$: C, 75.79; H, 7.11; N, 5.20. Found: C, 75.74; H, 7.08; N, 5.16%.

5.7. *3-Methoxy-7-tert-butyl-10H-phenothiazine (5f)*

Yield 72%, m.p. 97 °C; IR (KBr) cm^{-1}: 3330 (NH), 1325 (C−N), 657 (C−S−C); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.28 (s, 9H, *tert*-butyl), 3.64 (s, 3H, OCH_3), 7.21–8.68 (m, 6H, Ar−H), 9.92 (s, 1H, NH); MS: m/z 285; Anal. calcd. for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.58; H, 6.75; N, 4.98%.

5.8. *3-Chloro-7-tert-butyl-10H-phenothiazine (5g)*

Yield 68%, m.p. 153 °C; IR (KBr) cm^{-1}: 3333 (NH), 1330 (C−N), 658 (C−S−C); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (s, 9H, *tert*-butyl), 7.12–8.52 (m, 6H, Ar−H), 9.29 (s, 1H, NH); MS: m/z 290; Anal. calcd. for $C_{16}H_{16}NSCl$: C, 66.31; H, 5.56; N, 4.83. Found: C, 66.28; H, 5.50; N, 4.78%.

Acknowledgements

The authors thank the Professor and Head, Department of Chemistry, Saurashtra University, Rajkot for providing research facilities. Authors are thankful to CDRI Lucknow for spectral and analytical data.

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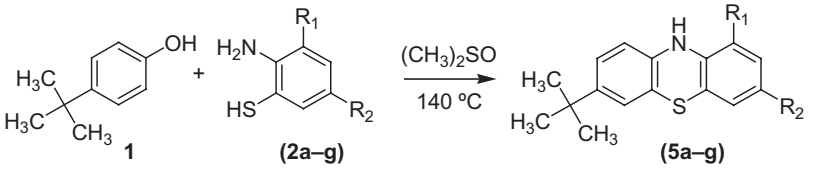

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