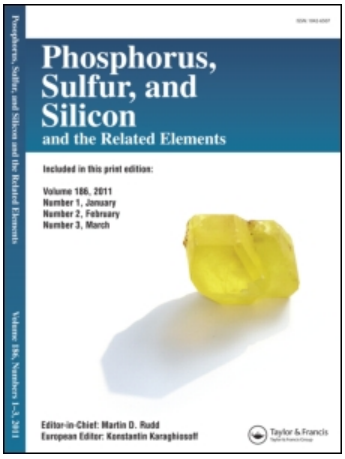



**Phosphorus, Sulfur, and Silicon and the Related Elements**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

# Synthesis and Biological Activity of 2-Hydroxy-N(5-methylene-4-oxo-2-aryl-thiazolidin-3-yl)-benzamide

Hasmukh S. Patel[a]; Sumeet J. Patel[a]
[a] Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar, India

Online publication date: 02 August 2010

**To cite this Article** Patel, Hasmukh S. and Patel, Sumeet J.(2010) 'Synthesis and Biological Activity of 2-Hydroxy-N(5-methylene-4-oxo-2-aryl-thiazolidin-3-yl)-benzamide', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 8, 1632 — 1639
**To link to this Article: DOI:** 10.1080/10426500903176521
**URL:** http://dx.doi.org/10.1080/10426500903176521

*Phosphorus, Sulfur, and Silicon*, 185:1632–1639, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903176521

Taylor & Francis
Taylor & Francis Group

# SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-HYDROXY-N(5-METHYLENE-4-OXO-2-ARYL-THIAZOLIDIN-3-YL)-BENZAMIDE

**Hasmukh S. Patel and Sumeet J. Patel**
*Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar, India*

***2-Hydroxy benzoic acid hydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding 2-hydroxy benzoic acid arylidene hydrazides (2a–h) in good yields. Cyclocondensation of compounds 2a–h with thioglycolic acid yields 2-hydroxy-N(4-oxo-2-aryl-thiazolidin-3-yl)-benzamides (3a–h). These 3a–h compounds are for the reacted with benzaldehyde in the presence of sodium ethanolate affords, giving 2-hydroxy-N(5-methylene-4-oxo-2-aryl-thiazolidin-3-yl)-benzamides (4a–h). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.***

***Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.***

**Keywords** Antibacterial activity; 2-hydroxy benzoic acid hydrazide; thiazolidin

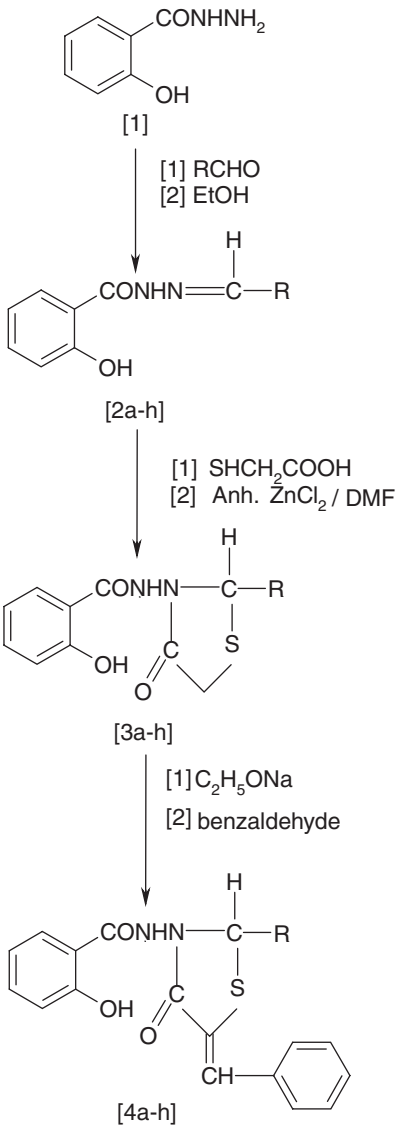


## INTRODUCTION

Hydrazides and their heterocyclized products display diverse biological activities including antibacterial, antifungicidal, analgesic, and anti-inflammatory properties.[1–15] These heterocyclic systems find wide use in medicine, agriculture, and industry. One of the hydrazides, 2-hydroxy benzoic acid hydrazide (i.e., salicylhydrazide) and its condensed products play a vital role in medicinal chemistry.[16–18] 4-Thiazolidinones and their arylidene compounds have good pharmacological properties.[19–23] 4-Thiazolidinones are also known to exhibit antitubercular,[24] antibacterial,[25] antifungal,[26] and anticonvulsant activities. Hence, it was thought of interest to merge both of thiazolidinone's and salicylhydrazide's moieties, which may enhance the drug activity of compounds to some extent, or they might possess some of the above-mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of salicylhydrazide containing thiazolidinone moiety. This article comprises the synthesis of 2-hydroxy-N(5-methylene-4-oxo-2-aryl-thiazolidin-3-yl)-benzamide. The synthetic approach is shown in Scheme 1.

Received 7 February 2009; accepted 10 July 2009.
The authors are thankful to Dr. J. S. Parmar, Head, Department of Chemistry, for providing laboratory facilities.

Address correspondence to H. S. Patel, Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar– 388 120, India. E-mail: hsp13152@rediffmail.co.in




Where, R = (a) $C_6H_5$ (e) 4-$CH_3$-$C_6H_4$

(b) 4-$OCH_3$-$C_6H_4$ (f) 3,4-$CH_2O_2$-$C_6H_4$

(c) 4-OH-$C_6H_4$ (g) 4-OH-3-$OCH_3$-$C_6H_3$

(d) 2-OH-$C_6H_4$ (h) 3,4-$C_2H_5$-$C_6H_4$

**Scheme 1**

## RESULTS AND DISCUSSION

It was observed that 2-hydroxy benzoic acid hydrazide (**1**), upon condensation with aromatic aldehydes, yields 2-hydroxy benzoic acid arylidene hydrazides (**2a–h**). The structures of **2a–h** were confirmed by elemental analysis and IR spectra, which showed an absorption band at 1620–1640 (C═N), 3030–3080 $cm^{-1}$ (C—H, of Ar.), 3450–3550 $cm^{-1}$ (—OH), 2815–2850 $cm^{-1}$ (—$OCH_3$), 2950, 1370 $cm^{-1}$ (—$CH_3$). $^1$H NMR: 6.95–7.91 (9H, m) (Ar—H), 11.200–11.209 (1H, s) (—OH), 11.800–11.809 (1H, s) (—CONH), 8.43–8.80 (1H, s) (—N═CH), **2e**; 2.41 (3H, s) (—$CH_3$), **2b**, **2g**; 3.90 (3H, s) (—$OCH_3$), **2h**; 4.09 (4H, q) ($CH_2$), 1.33 (6H, t) ($CH_3$), **2f**; 6.09 (2H, s) (—$OCH_2O$— cyclic). $^{13}$C NMR:117.9–118.1, 118.2–118.4, 121.8–122.0, 128.9–129.1, 129.2–129.4, 129.5–130.0, 131.2–131.5, 133.6–133.8, 133.9–134.3, 159.6–160.0 (Ar–10C), 163.5–163.8 (—CONH), 146.9–150.4 (—CH); **2b**, **2g**: 55.5–56.7 (—$OCH_3$); **2e**: 22.5 ($CH_3$); **2f**: 103.5 ($OCH_2O$ cyclic); **2h**: 65.3 ($OCH_2$), 15.0 ($CH_3$). The C, H, N analysis data of all compounds are presented in Table I.

The structures assigned to 2-hydroxy-N(4-oxo-2-aryl-thiazolidin-3-yl)-benzamides (**3a–h**) were supported by the elemental analysis and IR spectra showing an absorption bands at 1690 $cm^{-1}$ (C═O of thiazolidinone ring), 718 $cm^{-1}$ (C—S—C of thiazolidinone ring), 3075–3095 $cm^{-1}$ ($CH_2$ of thiazolidinone ring), 3030–3080 $cm^{-1}$ (C—H, of Ar.), 3450–3550 $cm^{-1}$ (—OH), 1660–1670 $cm^{-1}$ (—CONH) for **3a** compound.

$^1$H NMR: 3.85–3.95 (2H, s) (—$CH_2$ of the ring), 5.950–5.959 (1H, s) (—CH), 6.90–7.95 (9H, m) (Ar-H), 8.20–8.22 (1H, s) (—CONH), 11.200–11.209 (1H, s) (—OH), **3e**; 2.43 (3H, s) (—$CH_3$), **3b**, **3g**; 3.91 (3H, s) (—$OCH_3$), **3h**; 4.07 (4H q) ($CH_2$), 1.33 (6H, t) ($CH_3$), **3f**; 6.09 (2H, s) (—$OCH_2O$— cyclic). $^{13}$C NMR: 115.9–116.2, 121.3–121.5, 126.9–127.3, 127.4–127.6, 128.3–128.5, 128.6–128.8, 128.9–129.2 139.2–139.4, 156.9–157.5, 168.9–169.3 (Ar-10C), 38.9–39.5 (—$CH_2$ of the ring), 67.8–68.3 (—CH), 164.8–165.9 (—CONH), 168.9–169.9 (—CO of the ring); **3b**, **3g**: 56.0–56.4 (—$OCH_3$); **3e**: 22.9 ($CH_3$); **3f**: 102.2 ($OCH_2O$ cyclic); **3h**: 65.8 ($OCH_2$), 15.5 ($CH_3$). The C, H, N, S analysis data of all compounds are presented in Table II.

The IR spectra of **4a–h** closely resemble those of the corresponding **3a–h**, with the only discernable difference observed that the new band at 1625$cm^{-1}$ (—C═CH-Ar) is observed (but not strong) in all the spectra of **4a–h**, which might be responsible.

$^1$H NMR: 7.762 (1H, s) (—CH), 6.90–7.98 (9H, m) (Ar-H), 8.20–8.28 (1H, s) (—CONH), 5.350–5.359 (1H, s) (—OH), **4e**; 2.41 (3H, s) (—$CH_3$), **4b**, **4g**; 3.92 (3H, s) (—$OCH_3$), **4h**; 4.04, (4H, q) (—$CH_2$), 1.33 (6H, t) (—$CH_3$), **4f**; 6.09 (2H, s) (—$OCH_2O$ cyclic). $^{13}$C NMR: 117.9–118.2, 118.5–119.9, 121.6–121.9, 125.9–126.3, 127.3–127.6, 128.7–128.8, 128.9–129.1, 133.8–134.0, 141.9–142.3, 159.5–160.8 (Ar-10C), 143.4–143.7 (—C— of the ring), 73.1–73.4 (—CH of the ring), 114.9–115.3 (—$CH_2$), 166.5–166.7 (—CO), 166.8–166.9 (—CONH); **4b**, **4g**: 55.956.7 (—$OCH_3$); **4e**: 21.8 ($CH_3$); **4f**: 102.8 ($OCH_2O$); **4h**: 66.1 ($OCH_2$), 14.9 ($CH_3$). The C, H, N, S analysis data of all compounds are presented in Table III.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme 1. The IR data also direct for assignment of the predicted structure. The final structures of all compounds are confirmed by LC-MS. LC-MS data for all compounds are presented in Tables I–III.

**Table I** Analytical data and elemental analysis of compounds **2a–h**

| Compound | Molecular formula (Mol.wt.) | LC-MS LC-MS data | Yield | Mp* (°C) | Elemental analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | %C | | % H | | %N | |
| | | | | | Found | Calcd. | Found | Calcd. | Found | Calcd. |
| **2a** | $C_{14}H_{12}N_2O_2$ (240) | 246 | 89 | 232–236 | 69.97 | 70.00 | 4.97 | 5.00 | 11.64 | 11.67 |
| **2b** | $C_{15}H_{14}N_2O_3$ (270) | 277 | 82 | 240–241 | 66.65 | 66.67 | 5.15 | 5.19 | 10.34 | 10.37 |
| **2c** | $C_{14}H_{12}N_2O_3$ (256) | 262 | 79 | 236–238 | 65.60 | 65.63 | 4.66 | 4.69 | 10.95 | 10.94 |
| **2d** | $C_{14}H_{12}N_2O_3$ (249) | 255 | 85 | 231–235 | 69.97 | 70.00 | 4.97 | 5.00 | 11.64 | 11.67 |
| **2e** | $C_{15}H_{14}N_2O_2$ (254) | 261 | 81 | 238–240 | 70.85 | 70.87 | 5.48 | 5.51 | 11.00 | 11.02 |
| **2f** | $C_{15}H_{12}N_2O_4$ (284) | 289 | 83 | 240–244 | 63.35 | 63.38 | 4.19 | 4.23 | 9.83 | 9.86 |
| **2g** | $C_{15}H_{14}N_2O_3$ (270) | 278 | 80 | 241–246 | 66.64 | 66.67 | 5.15 | 5.19 | 10.33 | 10.37 |
| **2h** | $C_{18}H_{20}N_2O_4$ (328) | 338 | 78 | 253–257 | 65.81 | 65.85 | 6.06 | 6.10 | 8.51 | 8.54 |

*Uncorrected.

**Table II** Analytical data and elemental analysis of compounds **3a–h**

| Compound | Molecular formula (Mol.wt.) | LC-MS data | Yield | Mp* (°C) | Elemental analysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | %C | | %H | | %N | | %S | |
| | | | | | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. |
| **3a** | $C_{16}H_{14}N_2O_3S$ (314) | 321 | 65 | 210–212 | 61.12 | 61.15 | 4.44 | 4.46 | 8.90 | 8.92 | 10.14 | 10.19 |
| **3b** | $C_{17}H_{16}N_2O_4S$ (344) | 349 | 60 | 206–208 | 59.28 | 59.30 | 4.60 | 4.65 | 8.14 | 8.14 | 9.27 | 9.30 |
| **3c** | $C_{16}H_{14}N_2O_4S$ (330) | 340 | 57 | 155–158 | 58.15 | 58.18 | 4.20 | 4.24 | 8.46 | 8.48 | 9.68 | 9.70 |
| **3d** | $C_{16}H_{14}N_2O_4S$ (330) | 338 | 66 | 130–134 | 58.15 | 58.18 | 4.20 | 4.24 | 8.46 | 8.48 | 9.68 | 9.70 |
| **3e** | $C_{17}H_{16}N_2O_3S$ (328) | 336 | 62 | 167–170 | 62.17 | 62.20 | 4.86 | 4.88 | 8.50 | 8.54 | 9.73 | 9.76 |
| **3f** | $C_{17}H_{14}N_2O_5S$ (358) | 364 | 55 | 181–183 | 56.95 | 56.98 | 3.89 | 3.91 | 7.80 | 7.82 | 8.90 | 8.94 |
| **3g** | $C_{17}H_{16}N_2O_5S$ (360) | 366 | 49 | 154–156 | 56.65 | 56.67 | 4.41 | 4.44 | 7.75 | 7.78 | 8.85 | 8.89 |
| **3h** | $C_{20}H_{22}N_2O_5S$ (402) | 409 | 61 | 190–194 | 59.67 | 59.70 | 5.45 | 5.47 | 6.95 | 6.97 | 7.92 | 7.96 |

*Uncorrected.

**Table III** Analytical data and elemental analysis of compounds **4a–h**

| Compound | Molecular formula (Mol.wt.) | LC- MS data | Yield | Mp* (°C) | Elemental analysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | %C | | % H | | %N | | %S | |
| | | | | | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. |
| **4a** | $C_{17}H_{14}N_2O_3S$ (326) | 331 | 70 | 214–218 | 62.50 | 62.57 | 4.20 | 4.29 | 8.51 | 8.59 | 9.78 | 9.81 |
| **4b** | $C_{18}H_{16}N_2O_4S$ (356) | 361 | 64 | 220–221 | 60.63 | 60.67 | 4.41 | 4.49 | 7.80 | 7.87 | 8.90 | 8.99 |
| **4c** | $C_{17}H_{14}N_2O_4S$ (342) | 349 | 63 | 200–202 | 59.58 | 59.64 | 4.01 | 4.10 | 8.10 | 8.19 | 9.31 | 9.36 |
| **4d** | $C_{17}H_{14}N_2O_4S$ (342) | 350 | 55 | 206–208 | 59.58 | 59.64 | 4.01 | 4.10 | 8.10 | 8.19 | 9.31 | 9.36 |
| **4e** | $C_{18}H_{16}N_2O_3S$ (340) | 346 | 50 | 195–198 | 63.48 | 63.53 | 4.61 | 4.71 | 8.18 | 8.24 | 9.38 | 9.41 |
| **4f** | $C_{18}H_{14}N_2O_5S$ (370) | 377 | 59 | 207–210 | 58.30 | 58.38 | 3.70 | 3.78 | 7.50 | 7.57 | 8.60 | 8.65 |
| **4g** | $C_{18}H_{16}N_2O_5S$ (372) | 379 | 58 | 193—195 | 56.02 | 58.06 | 4.21 | 4.30 | 7.48 | 7.53 | 8.58 | 8.60 |
| **4h** | $C_{21}H_{22}N_2O_5S$ (414) | 419 | 55 | 215–217 | 60.81 | 60.87 | 5.20 | 5.31 | 6.70 | 6.76 | 7.69 | 7.73 |

*Uncorrected

## EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer, and $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples were taken on an LC-MSD-Trap-SL_01046.

### Preparation of 2-Hydroxy Benzoic Acid Arylidene Hydrazide (2a–h)

An equimolecular mixture of 2-hydroxy benzoic acid hydrazide (**1**), (0.01 mol) and the aromatic aldehydes (**a–h**) in ethanol (15 mL) was refluxed on a water bath for 1–2 h. The solid separated was collected by filtration, dried, and recrystallized from ethanol. The yields, melting points, and other characterization data of these compounds are given in Table I.



### Preparation of 2-Hydroxy-N-(4-oxo-2-aryl-thiazolidin-3-yl)-benzamide (3a–h)

A mixture of 2-hydroxy benzoic acid arylidene hydrazide (**2a–h**) (0.01 mol) in THF (30 mL) and mercaptoacetic acid (thioglycolic acid) (0.01 mol) with a pinch of anhydrous $ZnCl_2$ was refluxed for 12 h. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using a benzene/chloroform (8:2; v/v) mixture as eluent. The eluent was concentrated, and the product was crystallized from alcohol to give 4-thiazolidinones (**3a–h**), which were obtained in 50–65% yield. The yields, melting points, and other characterization data of these compounds are given in Table II.

### Preparation of 2-Hydroxy-N(5-methylene-4-oxo-2-aryl-thiazolidin-3-yl)-benzamide (4a–h)

An equimolar solution of N-(3-chloro-2-oxo-4-aryl-azetidin-1-yl)-2-hydroxy-benzamide) (**3a–h**) and benzaldehyde in dioxane (50 mL) in the presence of $C_2H_5ONa$ was refluxed for about 3 h. The solvent was removed in vacuo. The resulting product was recrystallized from methanol to yield compound **4a–h**. The yields, melting points, and other characterization data of these compounds are given in Table III.

## BIOLOGICAL SCREENING

### Antibacterial Activities

The antibacterial activities of all the compounds were studied against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*E.coli* and *Klebsiella promioe*) at a concentration of 50 $\mu$g/mL by agar cup plate method. For results, see the Supplemental Materials, Tables S1–S4, available online.

### Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp*, *Aspergillus niger*, *Botrydepladia thiobromine*, *Rhizopus nigricum*, and *Fusarium oxyporium*. For results, see the Supplemental Materials, Tables S1–S4, available online.

## REFERENCES


1. M. R. Shiradkar, K. K. Murahari, H. R. Gangadasu, T. Suresh, C. C. Kalyan, D. Panchal, R. Kaur, P. Burange, J. Ghogare, V. Mokale, and M. Raut, *Bioorg. Med. Chem.*, **15,** 3997 (2007).
2. Y. Janin, *Bioorg. Med. Chem.*, **15,** 2479 (2007).
3. E. Gursoy and N. Guzeldemirci-Ulusoy, *Eur. J. Med. Chem.*, **42,** 320 (2007).
4. M. R. Rao, K. Hart, N. Devanna, and K. B. Chandrasekhar, *Asian J. Chem.*, **20,** 1402 (2008).
5. K. B. Kaymakcıoglu, E. E. Oruc, S. Unsalan, F. Kandemirli, N. Shvets, S. Rollas, and D. Anatholy, *Eur. J. Med. Chem.*, **41,** 1253 (2006).
6. R. Kalsi, M. Shrimali, T. N. Bhalla, and J. P. Barthwal, *Indian J. Pharm. Sci.*, **41,** 353 (2006).
7. S. Gemma, G. Kukreja, C. Fattorusso, M. Persico, M. Romano, M. Altarelli, L. Savini, G. Campiani, E. Fattorusso, and N. Basilico, *Bioorg. Med. Chem. Lett.*, **16,** 5384 (2006).
8. D. Sriram, P. Yogeeswari, and K. Madhu, *Bioorg. Med. Chem. Lett.*, **15,** 4502 (2006).
9. A. Nayyar and R. Jain, *Curr. Med. Chem.*, **12,** 1873 (2006).
10. R. M. Fikry, N. A. Ismael, A. A. El-Bahnasawy, and A. A. Sayed El-Ahl, *Phosphorus, Sulfur, and Silicon*, **179,** 1227 (2006).
11. A. Walcourt, M. Loyevsky, D. B. Lovejoy, V. R. Gordeuk, and D. R. Richardson, *Int. J. Biochem. Cell Biol.*, **36,** 401 (2004).
12. M. G. Mamolo, V. Falagiani, D. Zampieri, L. Vio, E. Banfi, and G. Scialino, *Farmaco*, **58,** 631 (2003).
13. N. Terzioglu and A. Gursoy, *Eur. J. Med. Chem.*, **38,** 781 (2003).
14. S. G. Kucukguzel, E. E. Oruc, S. Rollas, F. Sahin, and A. Ozbek, *Eur. J. Med. Chem.*, **37,** 197 (2002).
15. S. Rollas, N. Gulerman, and H. Erdeniz, *Farmaco*, **57,** 171 (2002).
16. L. Q. Al-Mawsawi, R. Dayam, L. Taheri, M. Witvrouw, Z. Debyser, and N. Neamati, *Bioorg. Med. Chem. Lett.*, **17**(23), 6472 (2007).
17. C. Plasencia, R. Daym, Q. Wang, J. Pinski, T. R. Jr. Burke, D. I. Quinn, and N. Neamati, *Mol. Cancer Ther.*, **4**(7), 1105 (2005).
18. H. Zhao, N. Neamati, S. Sunder, H. Hong, S. Wang, G. W. Milne, Y. Pommier, and T. R. Burke Jr., *J. Med. Chem.*, **40**(6), 937 (1997).
19. K. C. Asati, S. K. Srivastava, and S. D. Srivastava, *Indian J. Chem.*, **45B,** 526 (2006).
20. A. Bishnoi, K. Srivastava, and C. K. M. Tripathi, *Indian J. Chem.*, **45B,** 2136 (2006).
21. N. P. Shetgiri and A. D. Chitre, *Indian J. Chem.*, **45B,** 1308 (2006).
22. R. Jadav, S. Srivastava, and S. D. Srivastava, *Chem. Asian J.*, **1,** 95 (2003).
23. S. Srivastava, A. Jain, and S. Srivastava, *J. Indian Chem. Soc.*, **83,** 1118 (2006).
24. K. M. Mistry and K. R. Desai, *E-Journal. Chem.*, **1**(4), 189 (2004).
25. H. S. Patel and H. J. Mistry, *Phosphorous, Sulfur, and Silicon*, **179,** 1085 (2004).
26. J. J. Bhatt, B. R. Shah, and N. C. Desai, *Indian J. Chem.*, **33B,** 189 (1994).