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The Conventional and MW Assisted Syntheses of Some Bridgehead Nitrogen Containing Triazolo-thiadiazoles by Cyclocondensation using N-Aryl Isocyanodichlorides and Antimicrobial Evaluation

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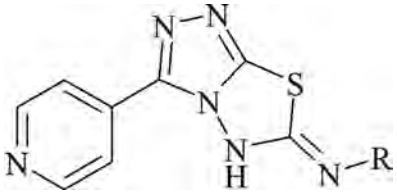
ABSTRACT The conventional and MW-assisted syntheses of 6-arylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazoles **(4)** have been carried out by interacting 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole **(2)** with *N*-aryl isocyanodichlorides **(3)** followed by the basification with dilute ammonium hydroxide. The acetylation of triazolo-thiadiazoles afforded acetyl derivatives. Structures of synthesized compounds have been established on the basis of chemical transformation, elemental analysis, equivalent weight determination, and infrared, ^{1}H nuclear magnetic resonance, mass spectral studies. Title compounds have been assayed for their antimicrobial activity against Gram-positive and Gram-negative microorganisms.



KEYWORDS Conventional, MW, Synthesis, Triazolo-thiadiazoles, Antimicrobial evaluation.

INTRODUCTION

Synthesis of organic compounds under the influence of microwave conditions has received considerable attention as a reliable and useful methodology for accelerating time-consuming reactions[1] and can be adapted for high-speed parallel synthesis of a library of bioactive compounds.[2,3] Heterocyclic compounds, especially those containing sulfur and nitrogen atoms, possess a wide variety of biological activities. Therapeutic effect of [1,2,4]-triazole and [1,2,4]-triazole-3-one containing compounds have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis, and hypertension.[4,5] Fused [1,2,4]-triazoles are found to possess diverse applications in the field of medicine.[6,7] Triazolo-thiadiazoles are found to show a broad spectrum of pharmacological properties such as antifungal, antibacterial, antiviral, anticonvulsant, anti-inflammatory, antituberculor, and analgesic activities.[8-11] These two fused systems are reported to possess significant central nervous system depressant, anthelmintic, and other pharmaceutical activities.[12,13] Synthetic applications of *N*-aryl isocyanodichlorides have been investigated earlier and shown to have enough potentiality in the synthesis of nitrogen- and sulfur-containing heterocyclic compounds.[14] In view of these findings and as a part of a wider program to provide alternative routes of synthesis,[15,16] we report herein the synthesis of substituted [1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazoles by conventional heating as well as MW irradiation.

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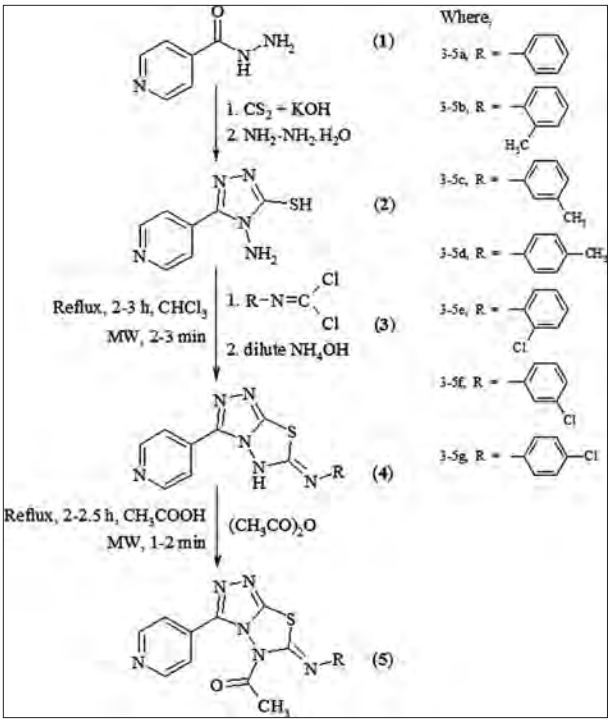
RESULTS AND DISCUSSION

The parent compound, isoniazid, was transformed into 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole **(2)** by interacting with carbon disulfide (0.01 mol) and potassium hydroxide (1M, 10 ml) followed by the addition of hydrazine hydrate (0.01 mol).[17] The compound (**2**) was then reacted with *N*-aryl isocyanodichlorides (**3a-g**) (0.01 mol) in boiling chloroform for 2–3 h. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. Cooling the reaction mixture and distilling off chloroform afforded sticky masses, which on washing with petroleum ether gave granular solids. These were acidic to litmus and on determination of equivalent weight found to be the hydrochlorides. These on basification with dilute ammonium hydroxide solution afforded free bases, 6-arylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazoles (**4a-g**). Simultaneously, compounds (**4a-g**) were also synthesized by MW irradiation under solvent-free conditions. Compounds (**4a-g**) on acylation with acetic anhydride afforded acetyl derivatives (**5a-g**). As compared to the conventional method, MW-assisted syntheses of compounds (**4a-g**) and (**5a-g**) required a very short period of time, and products were obtained with good yield (**Scheme 1**).



Scheme 1

Antimicrobial activity

The compounds (**4a-g**) were evaluated for their antibacterial activity by cup-plate diffusion method.[18,19] The bacterial organisms used included both Gram-positive as well as Gram-negative strains suc as *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Bacillus subtilis*, and *Proteus vulgaris*. Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU/ml, and each well (diameter 10 mm) was loaded with 0.1 ml of test compound solution (1000 µg/ml) in DMF so that concentration of each test compound was 100 µg/ml. The zones of inhibition were recorded after incubation for 24 h at 37°, using Vernier caliper. Inhibition zone record of the compounds clearly indicated that compounds **4b**, **4c**, and **4d** were highly active against *E. coli* and moderately active against *S. aureus* and *S. typhi*. Majority of the compounds were found to be inactive against *P. vulgaris* (**Table 1**).

To determine minimum inhibitory concentration (MIC), the serial dilution technique[20] was followed using nutrient broth medium. The MIC values of compounds **4b**, **4c**, and **4d**, which were determined against *E. coli*, found to be 78, 84, and 80 µg/ml, respectively.

Screening of these compounds, (**4b-g**) having the concentration 1% and 2%, for antifungal activity using paper disc method[21] showed that **4d** was highly active against *Aspergillus niger*, whereas other compounds showed low-to-moderate activity. Zones of inhibition were recorded after the incubation for 48 h at 37° (**Table 1**).

EXPERIMENTAL SECTION

The MW-assisted reactions were carried out using the commercial microwave (800 W). Melting points of all synthesized compounds were recorded using the Veego, VMP-D digital melting point apparatus, and are uncorrected. Chemicals used were of AR grade. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. IR spectra were recorded on Perkin-Elmer spectrophotometer in the range 4000–400 cm^{-1} in Nujol mull and as KBr pellet. The purity of the compounds was checked on silica gel-G plates by thin-layer chromatography (TLC).

The reagents N-aryl isocyanodichlorides were prepared by the exhaustive chlorination of aryl isothiocyanates in chloroform, maintaining the temperature at 10°. The reaction mixture was then diluted with petroleum ether (60–80°), and the solvent was distilled off under vacuum to get pale–yellow colored oily liquids (**3a-g**).

Synthesis of 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole (2)

The compound 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole (2) was prepared by the interaction of isoniazid (1) (0.01 mol) with carbon disulfide (0.01 mol) and potassium hydroxide solution (1 M, 10 ml) followed by the dropwise addition of hydrazine hydrate (0.01 mol) with constant stirring. Stirring was continued for 30 min at room temperature. The reaction mixture was cooled and poured in distilled water, and a white precipitate was obtained. It was crystallized from ethanol, (2) (85%), m.p. 145° (Found: C, 43.11; H, 3.31; N, 35.82; S, 16.08. $C_7H_7N_5S$ requires C, 43.52; H, 3.62; N, 36.26; S, 16.58%).

Table 1: Antibacterial and antifungal activity of compounds (4a-h)

Compounds	Antibacterial activity					Antifungal activity	
	E. coli	*S. aureus*	*S. typhi*	*B. subtilis*	*P. vulgaris*	*A. niger*	
						Concentration 1%	Concentration 2%
4a	+	+	–	–	+	–	–
4b	+++	++	++	+	–	+	+
4c	+++	++	++	+	–	++	++
4d	+++	++	++	+	+	+++	+++
4e	+	+	+	+	+	++	+
4f	++	+	+	+	+	–	+
4g	+	–	+	–	–	++	–

E. coli: Escherichia coli, S. aureus: Staphylococcus aureus, S. typhi: Salmonella typhi, B. subtilis: Bacillus subtilis, P. vulgaris: Proteus vulgaris, A. niger: Aspergillus niger –: Inactive (10 mm and less), +: Weakly active (11–15 mm), ++: Moderately active (16–20 mm), +++: Highly active (21 mm and above)

Conventional synthesis of 6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (4a)

The compound 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole (2) (0.01 mol) was reacted with *N*-phenyl isocyanodichloride (**3a**) (0.01 mol) in boiling chloroform medium over a water bath for 2.5 h. The evolution of hydrogen chloride gas was noticed. Cooling the reaction mixture and distilling off chloroform afforded a sticky mass, which on washing with petroleum ether (60–80°) gave a granular solid. It was acidic to litmus and on determination of equivalent weight found to be the hydrochloride. It on basification with dilute ammonium hydroxide solution afforded a free base, 6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (**4a**). It was crystallized from ethanol, (70%), m.p**.** 160°. (Found: C, 56.22; H, 3.30; N, 27.96; S, 10.22. $C_{14}H_{10}N_6S$ requires C, 57.14; H, 3.40; N, 28.57; S, 10.88%). This reaction was extended to synthesize the other compounds (**4b-g**). (**4b**) (70%), m.p**.** 210° (found: C, 58.02; H, 3.90; N, 27.01; S, 10.30. $C_{15}H_{12}N_6S$ requires C, 58.44; H, 3.89; N, 27.27; S, 10.38%); (**4c**) (75%), m.p**.** 169° (Found: C, 57.65; H, 3.70; N, 26.88; S, 10.13. $C_{15}H_{12}N_6S$ requires C, 58.44; H, 3.89; N, 27.27; S, 10.38%); (**4d**) (65%), m.p**.** 200° (found: C, 57.93; H, 3.82; N, 27.11; S, 9.97. $C_{15}H_{12}N_6S$ requires C, 58.44; H, 3.89; N, 27.27; S, 10.38%); (**4e**) (72%), m.p**.** 188° (Found: C, 50.22; H, 2.69; N, 25.02; S, 9.05. $C_{14}H_9N_6SCl$ requires C, 51.14; H, 2.73; N, 25.57; S, 9.74%); (**4f**) (70%), m.p**.** 224° (Found: C, 51.11; H, 2.74; N, 24.88; S, 9.51. $C_{14}H_9N_6SCl$ requires C, 51.14; H, 2.73; N, 25.57; S, 9.74%); (**4g**) (80%), m.p. 252° (found: C, 50.49; H, 2.66; N, 24.94; S, 9.23. $C_{14}H_9N_6SCl$ requires C, 51.14; H, 2.73; N, 25.57; S, 9.74%).

MW-assisted synthesis of 6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (4a)

A mixture of 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole (2) (0.01 mol) and *N*-phenyl isocyanodichloride (**3a**) (0.01 mol) was irradiated under microwave conditions for 2 min. An acidic solid mass was obtained, and it was basified with dilute ammonium hydroxide solution and crystallized from ethanol to give 6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (**4a**), (95%), m.p**.** 160°. The complete reaction was monitored by TLC and extended to synthesize the other compounds (**4b-g**) (90–98%).

Conventional synthesis of 5-acetyl-6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (5a)

The mixture of 6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (**4a**) (0.01 mol) and acetic anhydride (0.01 mol) in glacial acetic acid (10 ml) was refluxed for 2 hr. The reaction mixture was cooled and poured in a little crushed ice with water, and a cream-colored solid precipitated was crystallized from aqueous ethanol to give (**5a**), (70%), m.p**.** 218–220° (found: C, 57.19; H, 3.31; N, 24.88; S, 9.49. $C_{16}H_{12}N_6OS$ requires C, 57.14; H, 3.57; N, 25.00; S, 9.52%). This reaction was extended to synthesize the other compounds (**5b-g**). (**5b**) (68%), m.p**.** 201°; (**5c**) (70%), m.p**.** 227°; (**5d**) (65%), m.p**.** 202°; (**5e**) (78%), m.p**.** 183°; (**5f**) (70%), m.p**.** 118°; (**5g**) (75%), m.p**.** 254°.

MW-assisted synthesis of 5-acetyl-6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (5a)

The 6-phenylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazole (4a) (0.01 mol) and acetic anhydride (0.01 mol) were mixed together and irradiated under microwave conditions for 1.5 min. A cream-colored solid was obtained, and it was crystallized from aqueous ethanol to afford (**5a**), (92%), m.p**.** 219°. This reaction was extended to synthesize the other compounds (**5b-g**) (90–98%).

Spectral data of compounds (2), (4a), (4b), (5a), and (5b)

- (**2**): IR (KBr): 3423, 3370 (NH), 1682 (C=N), 1298 (C-N), 1210 (N-N), 758 cm^{-1} (C-S).[22]
- (**4a**): IR (KBr): 3423 (NH), 1607, 1557, 1518 (C=N), 1316 (C-N), 1217 (N-N), 708, 689 cm^{-1} (C-S); ^1H NMR ($CDCl_3$+DMSO-d_6): δ 5.84 (1H, s, NH), 7.06-8.75 (9H, m, Ar-H and Py-H); MS: m/z 293 (M^+-H), 217

(M^+-C_6H_5), 216 (M^+-C_5H_4N), 203 (M^+-N-C_6H_5), 138 (M^+-C_5H_4N-C_6H_5-H), 125 (M^+-C_5H_4N-N-C_6H_5).[22,23]

- (**4b**): IR (KBr): 3418 (NH), 1611, 1568, 1521 (C=N), 1331 (C-N), 1222 (N-N), 705, 693 cm^{-1} (C-S); ^1H NMR ($CDCl_3$+DMSO-d_6): δ 5.97 (1H, s, NH), 7.06-8.75 (8H, m, Ar-H and Py-H), 2.27 (3H, s, Ar-CH_3); MS: m/z 308 (M^+), 307 (M^+-H), 293 (M^+-CH_3), 230 (M^+-C_5H_4N), 217 (M^+-C_6H_4-CH_3), 203 (M^+-N-C_6H_4-CH_3).
- (**4d**): IR (KBr): 3427 (NH), 1617, 1587 (C=N), 1321 (C-N), 1247 (N-N), 708, 690 cm^{-1} (C-S); ^1H NMR ($CDCl_3$+DMSO-d_6): δ 5.81 (1H, s, NH), 6.94-8.48 (8H, m, Ar-H and Py-H).
- (**4e**): IR (KBr): 3422 (NH), 1626, 1551, 1523 (C=N), 1326, 1321 (C-N), 1236 (N-N), 689 cm^{-1} (C-S); ^1H NMR ($CDCl_3$+DMSO-d_6): δ 5.89 (1H, s, NH), 6.88-8.56 (8H, m, Ar-H and Py-H).
- (**5a**): IR (KBr): 1702 (C=O), 1608 (C=N), 1332, 1313 (C-N), 1248 (N-N), 704 cm^{-1} (C-S); ^1H NMR ($CDCl_3$+DMSO-d_6): δ 6.88-8.56 (9H, m, Ar-H and Py-H), 2.03 (3H, s, CO-CH_3).
- (**5b**): IR (KBr): 1698 (C=O), 1616 (C=N), 1327, 1306 (C-N), 1251 (N-N), 702 cm^{-1} (C-S); δ 7.03-8.63 (8H, m, Ar-H and Py-H), 2.31 (3H, s, Ar-CH_3), 2.11 (3H, s, CO-CH_3).

CONCLUSION

In the present work, conventional and MW-assisted synthesis of 6-arylimino-3-pyridin-4-yl-[1,2,4]-triazolo-(3,4-b)-[1,3,4]-thiadiazoles (**4a-g**) and their acetyl derivatives (**5a-g**) has been reported. The MW-assisted synthesis is quite simple, efficient, and completed within a short period of time with good yield as compared to conventional method. Antimicrobial study of synthesized compounds revealed that compounds (**4b**), (**4c**), and (**4d**) have very good antibacterial activities and compound (**4d**) has very good antifungal activities.

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REFERENCES

[1] Loupy, A. *Microwaves in Organic Synthesis*, 4th ed. Wiley, Weinheim, Germany, **2006**, p860.

[2] Shujiang, T., Xiaotong, Z., Jinpeng, Z., Jianing, X., Yan, Z., Qian, W., Runhong, J., Jing, B., Zhang, J., Yao, C. New potential biologically active compounds: Design and an efficient synthesis of N-substituted-4-aryl-4,6,7,8-tetrahydroquinoline-2,5 (1H, 3H)-diones under microwave irradiation, *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 2925.

[3] Cui, S.L., Lin, X.F., Wang, Y.G. Parallel synthesis of strongly substituted fluorescent polysubstituted 2,6-dicyanoaniline via microwave promoted multicomponent reaction, *J. Org. Chem.*, **2005**, *70*, 2866.

[4] Tozkoparan, B., Gokhan, N., Aktay, G., Yesilada, E., Ertan, M. 6-Benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones substituted with ibuprofen: Synthesis, characterization and evaluation of anti-inflammatory activity, *Eur. J. Med. Chem.*, **2000**, *35*, 743.

[5] Ikizler, A.A., Demirbas, N. A convenient synthesis of 4-amino-3,5-dialkyl-4*H*-1,2,4-triazoles, *J. Hetero. Chem.*, **1996**, *33*, 1765.

[6] Srivastava, M.K., Khare, R.K., Singh, H. Synthesis and fungicidal activity of some 5-(2-aminoalkanoyl)-8-aryl-4(5H)-oxo-1,2,4-triazolo[4,3-b]-1,4,2,6-dithiadiazine-6,6-dioxide derivatives, *Boll. Chim. Farm.*, **1999**, *138*, 511.

[7] Cablewski, T., Francis, C.L., Liepa, A.J. N,N-Dialkyl-N'-chlorosulfonyl chloroformamidines in heterocyclic synthesis VI the preparation of some fused [1,4,2,6]-dithiadiazine dioxides, *Aust. J. Chem.*, **2008**, *61*, 332.

[8] Mathew, V., Keshavayya, J., Vaidya, V.P., Giles, D. Studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues, *Eur. J. Med. Chem.*, **2007**, *42*, 823.

[9] Husain, A., Naseer, M.A., Sarafroz, M. Synthesis and anticonvulsant activity of some novel fused heterocyclic 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives, *Acta. Pol. Chem.*, **2009**, *66*, 135.

[10] Chawla, G., Kumar, U., Bawa, S., Kumar, J. Syntheses and evaluation of anti-inflammatory, analgesic and ulcerogenic activities of 1,3,4-oxadiazole and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives, *J. Enzyme Inhib. Med. Chem.*, **2012**, *27*, 658.

[11] Tozkoparan, B., Peri-Aytac, S., Gursoy, S., Gunal, S., Aktay, G. Novel 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives as dual analgesic/anti-inflammatory and antimicrobial agents, *Lett. Drug. Des. Discov.*, **2012**, *9*, 204.

[12] Prasad, D.J., Ashok, M., Karegoudar, P., Poojary, B., Holla, B.S., Kumari, N. S. Synthesis and antimicrobial activities of some new triazolo-thiadiazoles bearing 4-methylthiobenzyl moiety, *Eur. J. Med. Chem.*, **2009**, *44*, 551.

[13] Demirbas, A., Sahin, D., Demirbas, N., Karaoglu, S.A. Synthesis of some new 1,3,4-thiadiazol-2-ylmethyl-1,2,4-triazole derivatives and investigation of their antimicrobial activities, *Eur. J. Med. Chem.*, **2009**, *44*, 2896.

[14] Dyson, G.M., Harington, T. The action of chlorine on aryl thiocarbimides and the reactions of aryl isocyanodichlorides, *J. Chem. Soc.*, **1940**, 191–194.

[15] Deohate, P.P., Berad, B.N. Synthesis, characterization and antimicrobial study of substituted

bis-[1,2,4,5]-dithiadiazine and bis-[1,3,4]-thiadiazolidine derivatives, *J. Indian Chem. Soc.*, **2008**, *85*, 1050.

[16] Deohate, P.P., Berad, B.N. Synthesis, characterization and antimicrobial study of substituted bis-[1,3,4]-oxadiazole, bis-[1,3,4]-thiadiazole and bis-[1,2,4]-triazole derivatives, *J. Indian Chem. Soc.*, **2008**, *85*, 1153.

[17] Deohate, P.P., Kawle, P.R. Synthesis and antimicrobial screening of novel bis-triazolo-dithiadiazines containing bridgehead nitrogen, *J. Indian Chem. Soc.*, **2015**, *92*, 911.

[18] Barry, A.L. *The Antimicrobial Suspectibility Test; Principle and Practices*, Illus Lea and Fibiger, Philadephia, PA, USA, **1976**, p180.

[19] Cavanagh, F. *Analytical Microbiology*, Academic Press, New York, **1963**, p126.

[20] Nishina, C., Enoki, N., Tawata, S., Mori, A., Kobayashi, K., Fukushima, M. Antibacterial activity of flavonoids against *Staphylococcus epidermidis*, *Agric. Bio. Chem.*, **1987**, *51*, 139.

[21] Ananthanarayan, R., Jagram-Pancka, G.K. *Text Book of Microbiology*, 4th ed. Orient Longmans, New Delhi, **1990**.

[22] Colthup, N.B., Dally, L.H., Wiberly, S.E. *Introduction to Infrared and Raman Spectroscopy*, Academic Press, New York, **1964**.

[23] Silverstein, R.M., Bassler, G.C., Morrill, T.C. *Spectrometric Identification of Organic Compounds*, 4th ed. John Wiley & Sons, New York, **1981**.

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