December 2009 Volume 5 Issue 4

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(4), 2009 [424-428]

Synthesis of novel 2-(4-methoxy benzene sulfonyl)-1,3-dimethyl/ 1-methyl-3-phenyl/1,3-diphenylpropane-1, 3-dione and 2-(4-methylthio benzene sulfonyl)-1-methyl-3-phenyl/ 1,3-diphenyl/1-methyl-3-ethoxy propane-1,3-dione

Suresh Singh Chauhan[1*], Y.C.Joshi[2]

[1]Department of Chemistry, Faculty of Engineering & Technology, Mody Institute of Technology and Science, Lakshmangarh-332311, Sikar, (Raj.), (INDIA)

[2]Department of Chemistry, University of Rajasthan, Jaipur-302004, (INDIA)

E-mail : sureshsingh2288@gmail.com

Received: 7th October, 2009 ; Accepted: 17th October, 2009

ABSTRACT

An efficient synthesis of novel 2-(4-methoxy benzene sulfonyl)-1,3-dimethyl/1-methyl-3-phenyl/1, 3-diphenyl propane-1, 3-dione(IIa-c) and 2-(4-methylthio benzene sulfonyl)-1-methyl-3-phenyl/1, 3-diphenyl/1-methyl-3-ethoxy propane-1, 3-dione(IVa-c) in corporating 4-methoxy benzene sulfonyl/4-methylthio benzene sulfonyl nucleus is described.Compounds IIIa-c and IVa-c were synthesize by the reaction of acetyl acetone/benzoyl acetone/dibenzoylmethane/ethylacetoacetate(Ia-c & IIIa-c) with 4-methoxy benzene sulfonyl chloride 1 and 4-methylthio benzene sulfonyl chloride 2 in presence of sodium methoxide.Formation of 1 and 2 was achived by the reaction of anisol/thioanisole with chlorosulphonic acid.

KEYWORDS

1,3-diketones (β-diketones);
1,3-ketoester;
Sodium methoxide;
Chlorosulfonic acid;
Sulfonyl group.

INTRODUCTION

1,3-diketones (β-diketones) have been important intermediates in synthetic organic chemistry[1] as well as metallocomplexes and related areas of technology[2]. 1,3-diketones compounds and their derivatives have been the most versatile and frequently used in heterocyclic synthesis[3]. They play a very important role as building blocks for construction of a broad diversity of natural products, including aromatics and many heterocycles[4]. 1,3-diketones serves as precursors for the synthesis of versatile intermediates for obtaining large number of biologically active heterocyclic compounds such as diazepines, benzodiazepines, benzothiazepines, isoxazoles, pyrazoles, imidazoles and benzimidazoles[5].

Many naturally occurring 1,3-diketones, even such simple once as dibenzoylmethane and n-tritriacontane-16, 18-dione possess a broad spectra of biological activity. These 1,3-diketones and their closet structural derivatives appear in many plants, for example, in *Eucalyptus* leafs and *Licorice*[4]. Other long chain aliphatic 1,3-diketones are found in *Vanilla*beans and *Sunflower* pollen[6]. All mentioned 1,3-diketones are powerful natural antioxidants and possess prominent anticancer properties with minimal toxicity[7]. Four 1,3-

diketones isolated from *Nicotiana tobacum* also showed antioxidant activity[8]. That is why intensive investigations of biological properties of both natural and synthetic 1,3-diketones are of current interest to medicinal chemistry[9].

Compounds containing sulfonyl group have also been a research focus as a result of their biological important and chemical applications[10]. Sulfones occupy a unique position in the drug industry with their antimalarial[11], bactericidal[12] and antitubercular activity against *Mycobacterium tuberculosis*[13]. Antimalarial activity of Acedapson(4,4-diacetyl diaminodiphenyl sulfone) has been studied against *Plasmodium berghii*[11]. The sulfone Depsone(4,4-diaminodiphenyl sulfone) is well known antileprotic drug[14].Arylsulfonyl substituents have been used as protecting groups for oxygen and nitrogen functionalities[15]. Promizole is the most effective aryl heterocyclic sulphone drug[16].

Perusal of literature revealed that only a few diketones having sulfonyl group have so far been synthesized. These observations of sulfones and 1,3-diketones compounds prompted us to synthesize new pharmacologically active compounds bearing a sulfonyl group. For this purpose we have chosen 4-(methoxy) benzene sulfonyl chloride and 4-(methylthio) benzene sulfonyl chloride as starting moiety.

RESULT AND DISCUSSION

As an avenue to such species, anisol and thioanisole was sulphonated with $ClSO_3H$ to afford the sulfonyl compounds (1 & 2). The latter was condensed with different 1,3-diketones/1,3-ketoester (Ia-c & IIIa-c) in the presence of sodium methoxide to yield 1,3-diketones/1,3-ketoester (IIa-c & IVa-c). The structure of the compounds (IIa-c & IVa-c) has been established by IR, ^1H NMR, ^{13}C NMR and elemental analysis.

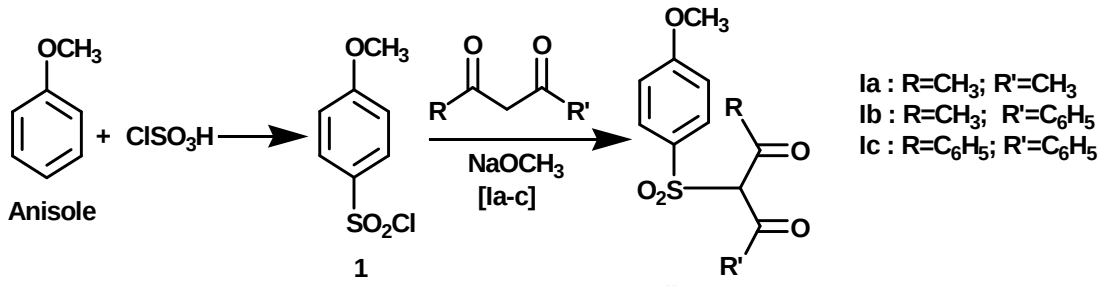
EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Nicolet-Megna FT-IR 550 spectrophotometer in KBr pellets. The ^1H NMR and ^{13}C NMR spectra were scanned in $CDCl_3$ on a DRX-300 spectrometer at 300.13, using TMS as an internal standard. The Mass spectra were recorded on a Jeol D-300 spectrometer. TLC checked the purity of compounds.

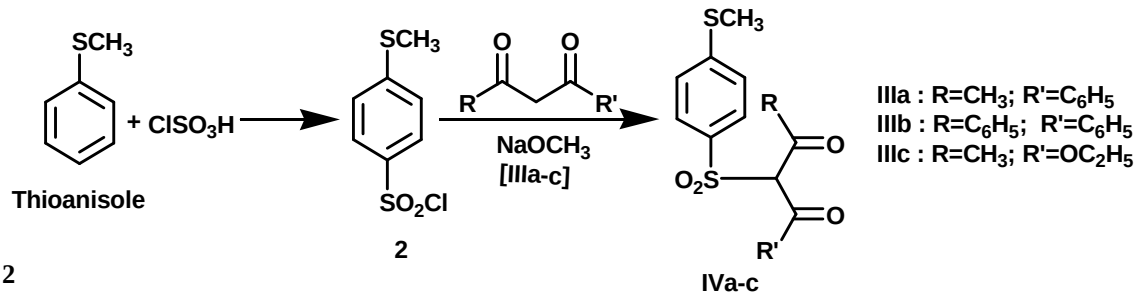
Synthesis of 4-methoxy benzene sulphonyl choride

Pure chlorosulphonic acid (11.9ml, 0.05M) was taken in a three necked round bottomed flask (100ml) fitted with a reflux condenser, dropping funnel and mercury seal with mechanical stirrer. The temperature of the flask was maintained below 5°C by placing it in an ice bath (ice-salt mixture). To this anisole (methoxy benzene) (5.44ml, 0.05M) was added dropwise using dropping funnel with continuous stirring. The excess of HCl gas was removed during the reaction.

After the complition of the reaction, mixture was

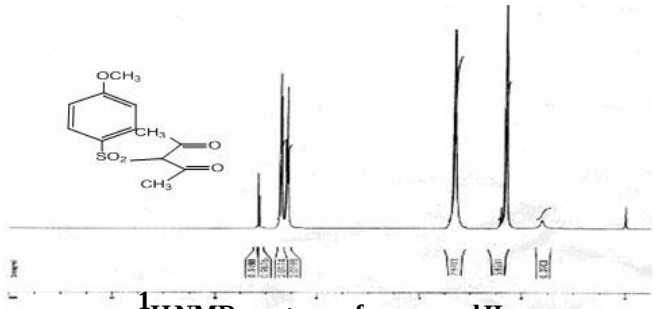


Scheme 1

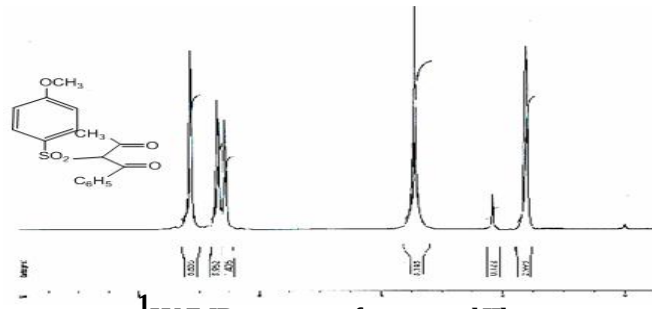


Scheme 2

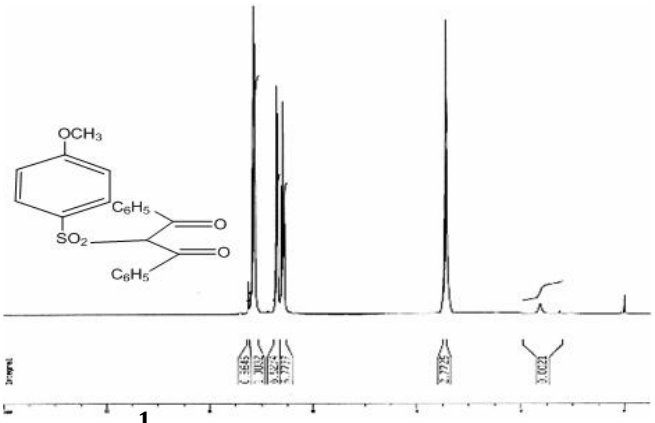
Full Paper



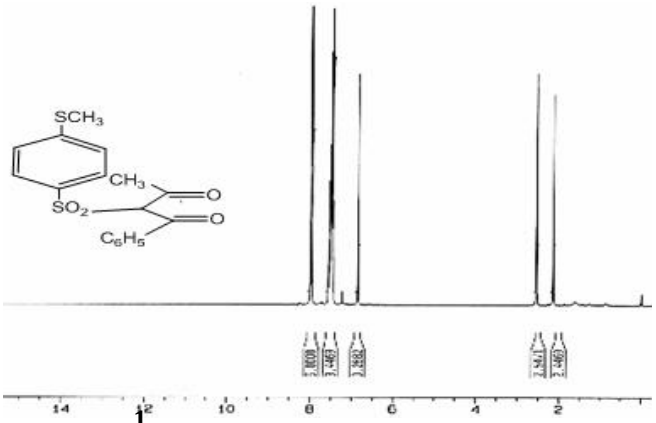
^{1}H NMR spectrum of compound IIa



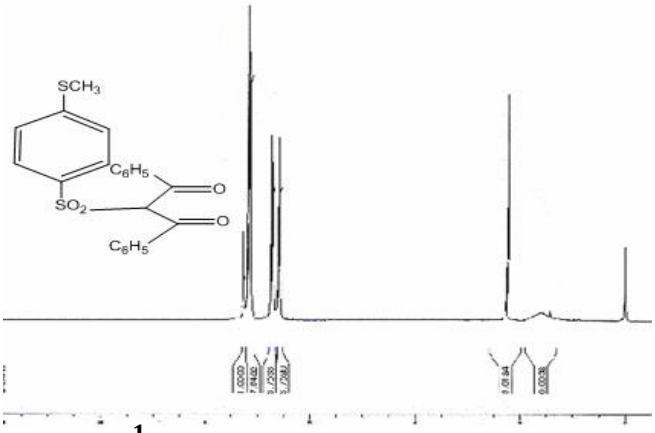
^{1}H NMR spectrum of compound IIb



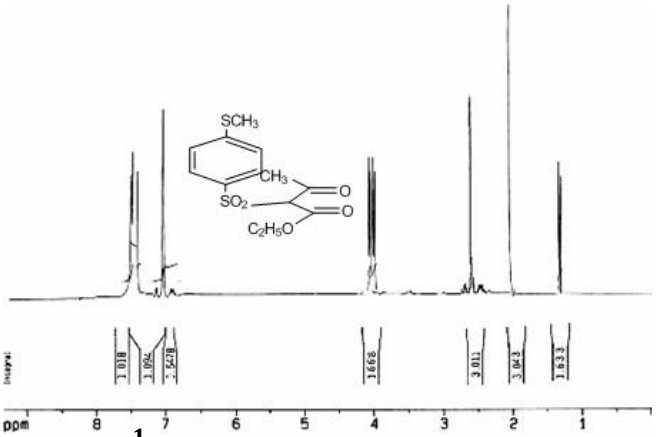
^{1}H NMR spectrum of compound IIc



^{1}H NMR spectrum of compound IVa



^{1}H NMR spectrum of compound IVb



^{1}H NMR spectrum of compound IVc

kept overnight in refrigerator. The reaction mixture was poured into crushed ice. The white solid obtained was filtered, washed 4-5 times with ice-cold water and dried. The crude solid was dissolved in a mixture of equal volume of benzene and acetone. The solution was filtered, concentrated and then kept at room temperature overnight. Crystalline 4-methoxy benzene sulphonyl chloride separated out. (m.p. 41°**C**, yield 8.36g, 81%).

Synthesis of 4-methyl thiobenzene sulphonyl chloride

Placed chlorosulphonic acid (1.20ml, 0.02M) in a three-necked flask, fitted with a reflux condenser, dropping funnel and mercury seal with mechanical stirrer. The temperature of the flask was maintained below 5°C by placing it in an ice bath (ice-salt mixture). To this thioanisole (methyl thiobenzene) (2.33ml, 0.02M) was added dropwise using dropping funnel with continuous stirring. The excess of HCl gas was removed during the reaction. After addition, the reaction mixture was kept overnight in refrigerator.

The reaction mixture was prured into crushed ice. The white solid obtained was filtered, washed 4-5 times with ice-cold water and dried. The crude solid was dissolved in a mixture of equal volume of benzene and acetone. The solution was filtered, concentrated and then kept at room temperature overnight. Crystalline

4-methylthio benzene sulphonyl chloride separated out. (m.p. 132°C, yield-2.53g, 57 %).

Generalized preparation of substitued 1,3-diketones (IIIa-c & IVa-c)

Placed acetylactone (1ml, 0.01M)/benzoylacetone (1.62g, 0.01M)/dibenzoylmethane (2.24g, 01M)/ ethylacetoacetate (1.27g, 0.01 M) and sodium methoxide (0.54g, 0.01M) in a dry round bottomed flask fitted with a guard tube and stirred for one hour on a magnetic stirrer at 50°C-60°C, until a creamy mass was obtained. The sulphonyl chloride derivative (1 & 2) (2.06g, 0.01M & 2.39g, 0.01M) was then added in small portion and dry toluene (5ml) was added as solvent to effect proper stirring of the reaction mixture.

The reaction mixture was refluxed at a temperature of 110°C for about thirty/thirty-two hours. The completion of the reaction was monitored through TLC. After the reaction was completed the reaction mass was cooled and toluene was removed under reduced pressure. The reaction mixture was extracted using chloroform and then washed with water. The chloroform layer was then dried over anhy. Na_2SO_4. The chloroform was distilled off and purification of the compound was done by column chromatography using silica gel as absorbent and $CHCl_3$:MeOH (9:1) as mobile phase. The product was recrystallized from pet ether/ benzene:acetone(1:1)/absolute alcohol. Purity of the diketone was checked through TLC using (petroleum ether:acetone, 7:3/benzene:ethanol:ammonia, 7:2:1) upper layer as mobile phase. Spectral data for selected products IIIa-c and IVa-c.

2-(4-methoxy benzene sulfonyl)-1, 3-dimethyl propane-1,3-dione(IIa)

M.p.:110°C ; yield 51% ; Anal.Calcd.of $C_{12}H_{14}O_5S$. Calcd: C, 53.33; H, 5.19. Found: C, 53.04; H, 4.78. IR (KBr): 3030, 2910, 1705, 1305, 1250, 1145, 1060cm^{-1}. ^{1}H NMR(300MHz, $CDCl_3$) δ 7.08 (dd, J=7.6Hz, 4H), 3.55(s, 3H), 2.07(s, 6H), 7.12(s, 1H); ^{13}C NMR(300MHz, $CDCl_3$): δ 204.94, 132-130, 113.70, 102.70, 65.26, 55.37, 26.85.

2-(4-methoxy benzene sulfonyl)-1-methyl-3-phenyl propane-1,3-dione(IIb)

M.p.:95°C; yield47%; Anal.Calcd.of $C_{17}H_{16}O_5S$. Cacld: C, 61.44; H, 4.81. Found: C, 61.09; H, 4.56. IR (KBr): 3035, 2875, 1715, 1305, 1248, 1138, 1058cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.30-8.05 (m, 9H), 3.78 (s, 3H), 2.10 (s, 3H), 7.13 (s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 204.94, 182, 132-131, 113.70, 98.81, 65.26, 55.37, 26.70.

2-(4-methoxy benzene sulfonyl)-1,3-diphenyl propane-1,3-dione(IIc)

M.p.: 55°C; yield 56%; Anal.Calcd.of $C_{20}H_{18}O_5S$. Calcd: C, 64.86; H, 4.86. Found: C, 64.10; H, 4.46. IR (KBr): 3010, 1725, 1310, 1245, 1160, 1055cm^{-1}, ^{1}H NMR(300MHz, $CDCl_3$): δ 6.80-7.40(m, 10H), 6.71(dd, J=6.7Hz, 4H), 3.54(s,3H), 7.19(s,1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 182, 134-131, 128.62, 113.70, 94.34, 65.26, 55.37.

2-(4-methylthio benzene sulfonyl)-1-methyl-3-phenyl propane-1,3-dione(IVa)

M.p.:104°C; yield46%; Anal.Calcd. of $C_{17}H_{16}O_4S_2$. Calcd: C, 58.62; H, 4.60. Found: C, 58.22; H, 4.24. IR (KBr): 2880, 1715, 1415, 1320, 1300, 1170cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.00-8.00(m, 9H), 2.52(s, 3H), 2.10(s, 3H), 6.90(s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 184, 142.56, 1350, 133–127, 94.34, 14.18.

2-(4-methylthio benzene sulfonyl)-1, 3-diphenyl propane-1,3-dione (IVb)

M.p.: 83°C; yield 51%; Anal.Calcd. of $C_{12}H_{18}O_4S_2$. Calcd: C, 64.39; H, 4.39. Found: C, 64.03; H, 4.07. IR(KBr): 3010, 1720, 1395, 1305, 1990, 1155 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.24(dd, J=7.9Hz, 4H), 7.32-8.01(m, 10H), 2.63(s, 3H), 7.16(s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 204.94, 182, 142.56, 133–127, 98.81, 14.82.

2-(4-methylthio-benzene sulfonyl)-1-methyl-3-ethoxy-propane-1,3-dione (IVc)

M.p.:103°C; yield 47%; Anal.Calcd. of $C_{12}H_{16}O_5S_2$. Calcd: C, 49.36; H, 5.06. Found: C, 48.97; H, 4.73. IR (KBr): 3045, 2885, 1745, 1435, 1340, 1325, 1235, 1140, 1110 cm^{-1}; ^{1}H NMR (300MHz,$CDCl_3$): δ 7.80(dd, J=8.04Hz, 4H), 2.81(s, 3H), 1.64(t, J=7.1, 3H), 4.32(q, J=7.1, 2H), 2.14(s, 3H), 7.2(s, 1H); ^{13}C NMR (300MHz, $CDCl_3$): δ 204.94, 161.57, 142.56, 134–127, 93.13, 63.52, 26.72, 14.82, 14.12.

Full Paper

ACKNOWLEDGMENT

Authors are thankful to the Dean, FET-MITS, Lakshmangarh and Head, Department of Chemistry, University of Rajasthan Jaipur, for providing laboratory facilities. Authors are also thankful to Central Drug Research Institute, Lucknow and IIT, Delhi for providing spectral data.

REFERENCES

[1] (a)G.Kollenz, T.S.Dalvi, C.O.Kappe, C.Wentrup; Arkivoc, **1(1)**, 74-79 **(2000).** (b)J.Christoffers, H.Oertling, P.Fischer, W.Frey; Tetrahedron, **59**, 3769-2778 **(2003).** (c)H.J.Cristau, X.Marat, J.P.Vors, J.L.Pirat; Tetrahedron Lett., **44**, 3179-3181 **(2003).** (d)A.R.Katritzky, A.Siliva, D.O.Tymoshenko, G.Qiu, S.K.Nair, P.J.Steel; Arkivoc, **I**, 36-42 **(2003).** (e) F.S.Falsone, C.O.Kappe; Arkivoc, **ii**, 122-134 **(2001).** (f)C.R.Hauser, F.W.Swamer, J.T.Adams; Org.React., **8**, 59 **(1954).** (g)S.Kotha, E.Manivannan; Arkivoc, **3**, 67-76 **(2003).** (h)H.Paulsen, S.Antons, A.Brandes, M.Loegers, S.N.Muller, P.Naab, C.Schmeck, S.Schneider, Stoltefuss; J.Angew.chem.Int.Ed., **38**, 3373 **(1999).** (i)A.M.Yoshida, K.Fujikawa, S.Sato, S.Hara; Arkivoc, **vi,** 36-42 **(2003).** (j)T.H.Black; Org.Proc.Int., **21**, 179 **(1989).** (k)G.Stork, A.Brizzolara, H.Landesman, J.Szmuszkovicz, R.Terrell; J.Am.chem.Soc., **85**, 207 **(1963).** (l)I.Bennett, N.J.P.Broom, R.Cassels, J.S.Elder, N.D.Masson,P.O'Hanlo; J.Bioorg.Med.chem.Lett., **9**, 1847 **(1999).**

[2] (a)F.Bonati; Organomet.chem.Rev., **1**, 379 **(1966).** (b)R.M.Pike; Coord.chem.Rev., **2**, 163 **(1967).** (c)Comprehensive Coordination Chemistry, Vol. **2**; Wilkinson,G.Ed.Pergamon Press, **(1987).** (d)S.Nigam, B.S,Joshi, S.S.Chauhan, Y.C.Joshi; J.Indian Chem.Soc., **82**, 441-442 **(2005).** (e)K.C.Joshi, V.N.Pathak; Coord.Chem.Rev., **22**, 37 **(1977).** (f)R.C.Mehrotra, R.Bohra, D.P.Gaur; Metal β-Diketonates and Allied Derivatives, Academic Press, New York, **(1978).** (g)I.V.Svistunova, N.P.Shapkin, Svistunov; Russian Journal of General Chemistry, **71**, 1355 **(2001).** (h)Y.Nakano, A.Baba, T.Adochi, T.Noguchi; Inorg.Chim.Acta, **321**, 149 **(2001).**

[3] (a) B.Stanovnik, Svete; J.chem.Rew., **104**, 2433 **(2004).** (b)H.Sheibani, M.R.Islami, H.Khabazzadeh, K.Saidi; Tetrahedron, **60**, 5932 **(2004).** (c)H.Sheibani, M.H.Mosslemin, S.Behzadi, M.R.Islami, K.Saidi; Synthesis, 435 **(2006).**

[4] (a)T.M.Harris, C.M.Harris; Tetrahedron, **33**, 2159 **(1977).** (b)G.P.Ellis; Chromenes, Chromanones,and Chromones, Wiley: New York, **(1977).** (c)Mann; J.Secondary Metabolism:Second Ed: Oxford Univerisity Press: New York, **(1987).**

[5] (a)A.Nagpal, R.Unny, P.Joshi, Y.C.Joshi; Heterocyclic Communications, 589 **(2001).** (b)R.Unny, P.Joshi, M.P.Dobhal, Y.C.Joshi; Heterocyclic Communications, **2**, 171 **(2003).** (c)J.Bhagwan, Y.C.Joshi, R.P.Tyagi, B.C.Joshi, H.N.Mangal; J.Institution of Chemist, **55**, 58 **(1983).** (d)R.K.Saini, Y.C.Joshi, P.Joshi; Heterocyclic Communications, **13**, 219 **(2007).** (e)S.Nigam, Y.C.Joshi; Heterocyclic Communications, **9**, 405 **(2003).** (f)Y.C.Joshi, P.Joshi, S.S.Chauhan, S.Nigam; Heterocyclic Communications, **10**, 249 **(2004).** (g)S.Nigam, Y.C.Joshi; Phosphorus, Sulfur and Silicon, **178**, 1583 **(2003).** (h)R.Kumar, Y.C.Joshi; Arkivoc, **xiii**, 142-149 **(2007).** (i)C.L.Perrin, Nielson; J.B.Annual Rev.Phys.Chem., **48**, 511 **(1997).**

[6] (a)T.Osawa, Y.Sugiyama, M.Inayoshi, S.Kawakishi; ACS Symposium Series, **183**, 547 **(1994).** (b)C.C.Lin, Y.P.Lu, V.R.Lou, C.T.Ho, H.H.Newmark, C.MacDonald, K.W.Singletary, M.T.Huang; Cancer Lett., **125**, 168 **(2001).**

[7] (a) B.Ramaroson-Raonizafinimanana, E.M.Gaydou, I.Bombarda; J.Agric,Food.chem., **48**, 4739 **(2000).** (b)S.Schulz, C.Arsene, M.Tauber, J.N.McNeil; Phytochemistry, **54**, 325 **(2000).**

[8] (a) M.Hirose, K.Ozaki, K.Takaba, S.Fukushima, N.Ito; Carcinogenesis, **12**, 1917 **(1991).** (b)K.Takaba, M.Hirose, Y.Yoshida, J.Kimura, N.Ito; Cancer Lett., **39**, 113 **(1997).**

[9] T.Matsuzaki, Koiwai; Agric.Biol.Chem., **52,** 2341 **(1998).**

[10] (a)C.Hansch, P.G.Sammes, J.B.Taylor; Comprehensive Medicinal Chemistry, PergamonPress:Oxford, **(1990)**, vol.**2**, Chapter 7.1. (b)W.R.Roush, S.L.II.Gwalfney, J.Cheng, K.A.Scheidt, J.H.McKerrow, E.Hansell; J.Am.Chem.Soc., **120**, 10994 **(1998).**

[11] P.E.Thompson, B.S.Olszewski, J.A.Waitz; Am.J.Trop.Med.Hyg., **14**, 343 **(1965).**

[12] D.J.N.Hossack; Ann.Int.Pasteur, **103**, 866 **(1962).**

[13] S.K.Gupta; J.Sci.Ind.Res.C, **20**, 173 **(1961).**

[14] (a) A.G.Vorm, B.Siegfried; Swiss, **108**, 234 **(1944)**; Chem.Abstr, **43**, 4297 **(1949).** (b)B.C.Jain, B.H.Lyer, P.C.Guha; Science and Culture, **11**, 568 **(1946)**, Chem..Abstr., **40**, 4687, **(1946).** (c)E.Titus, Bernstein; J.Ann.N.Y.Acad.Sci, **52**, 719 **(1949).**

[15] J.F.O'Connel, H.Rapoport; J.Org.Chem., **57**, 4775 **(1992).**

[16] L.L.Bambas; J.Am.Chem.Soc., **67**, 671668 **(1945).**