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Heterogeneous $NaHSO_4 \cdot SiO_2$ catalyzed 'one-pot' synthesis and *in vitro* antibacterial and antifungal activities of pyridino-1,2,3-thiadiazoles

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A 'one-pot' synthesis of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles (**11–15**) using $NaHSO_4 \cdot SiO_2$ heterogeneous catalyst in dry media under microwave irradiation by a simple synthetic strategy is described. Among the synthesized 1,2,3-thiadiazoles, compounds having electron withdrawing chloro- and fluoro- functional group on the aryl moiety **14** and **15** exerted a wide range of modest antibacterial and antifungal activity *in vitro* against the tested organisms. The obtained results may be used as a key step for the building of novel chemical compounds with interesting antimicrobial profiles comparable with that of the standard drugs.

Keywords: 3,3-dimethyl-2,6-diarylpiperidin-4-one; 1,2,3-thiadiazoles; $NaHSO_4 \cdot SiO_2$ heterogeneous catalyst; antibacterial activity and antifungal activity

1. Introduction

1,2,3-Thiadiazoles were useful intermediates in organic synthesis (*1*), as well as an important class of biologically active compounds (*2–5*). For Instance, 4,5-bis(4′-methoxyphenyl)-1,2,3-thiadiazoles was found to be an active inhibitor of collagen-induced platelet aggregation *in vitro* (*6*). Earlier, 1,2,3-thiadiazoles were synthesized from the reaction of α-methylene (or ethyl) hydrazones (*7*). Many methods have been developed for the synthesis of 1,2,3-thiadiazoles, of which the Hurd–Mori cyclization of α-methylene ketones was the most convenient methodology (*8–13*).

Piperidin-4-one nucleus have received extensive attention in the past and recent years because of their diverse biological activities, including antiviral, antitumor (*14, 15*), central nervous system (*16*), local anesthetic (*17*), anticancer (*18*), and antimicrobial activity (*19*). Their derivative piperidine is also biologically important and acts as a neurokinin receptor antagonist (*20*) and an analgesic and anti-hypertensive agent (*21*). Recently, there have been a great deal of interest in exploiting more than one proximal functional groups for designing novel structures capable of performing a variety of functions. One such functionality was α-keto methylene group, which have been used as a building block for 1,2,3-thiadiazoles.

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The microwave-induced rate acceleration technology have become a powerful tool in organic synthesis in view of the mild, clean, and convenient methodology and the enhanced selectivity of the reaction processes in comparison with conventional solution reactions, and the associated ease of manipulation (*22–24*). Chemical reactions were accelerated essentially because of selective absorption of microwave energy by polar molecules, which are inert to the microwave dielectric loss. Among them, heterogeneous reactions facilitated by supported reagents on various mineral oxides have received special attention recently (*25, 26*).

Owing to our interest in synthesizing fascinating pharmacological and therapeutic important compounds under solid-state reactions (*27, 28*), we attempt and succeed now to use silica gel-supported sodium hydrogen sulphate ($NaHSO_4 \cdot SiO_2$) as a heterogeneous catalyst for the one-pot conversion of 3,3-dimethyl-2,6-diaryl-piperidin-4-ones **(1–5)** to 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles **(11–15)** in dry media under microwave irradiation.

2. Results and discussion

2.1. *Chemistry*

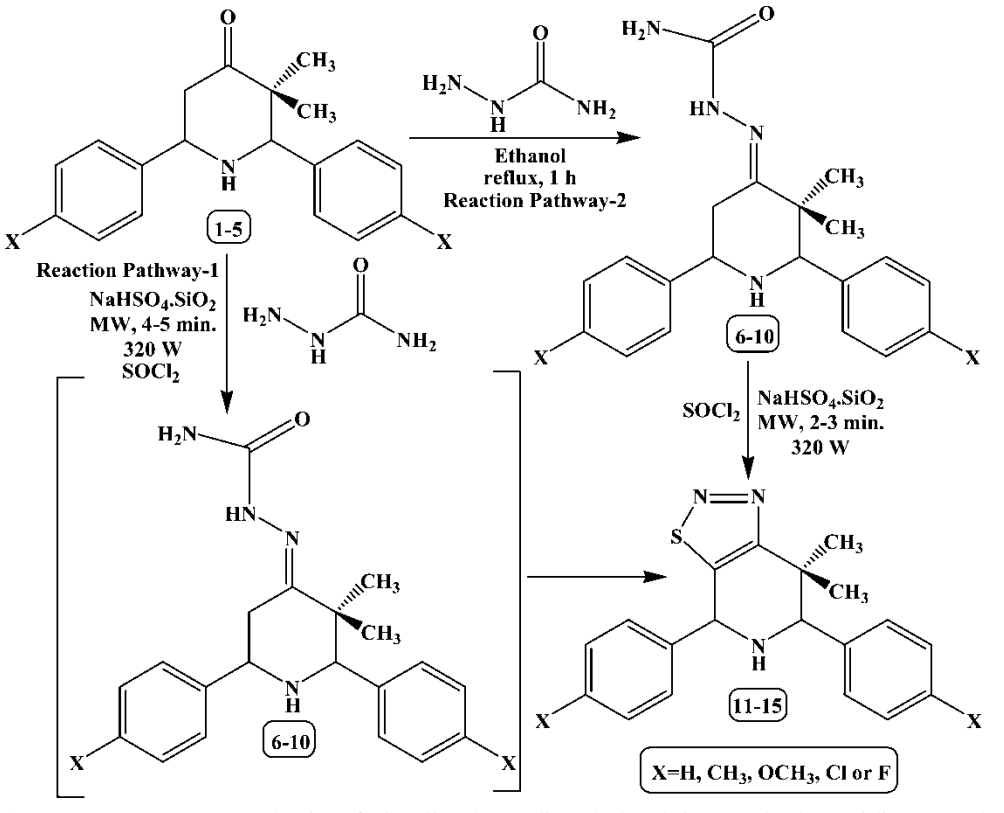
The only classical method available for the synthesis of 1,2,3-thiadiazoles was the conversion of semicarbazones of respective ketones by thionyl chloride in dichloromethane. There were some problems associated with the above synthesis, such as severe conditions, very low yields for the reaction, difficulty in separating the products from the system, and longer reaction times. In the present 'one-pot' procedure, a treatment of 0.01 mole of 3,3-dimethyl-2,6-diaryl-piperidin-4-ones, 0.01 mole of semicarbazide, and 0.01 mole of thionyl chloride along with a catalytic amount of $NaHSO_4 \cdot SiO_2$ (50 mg) affords the corresponding 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-thiadiazoles **(11–15)** (Scheme 1) in high yields when compared with general conditions (Table 1) in dry media under microwave (MW) irradiation. $NaHSO_4 \cdot SiO_2$ catalyst was shown to be one of the most efficient MW absorber with a very high specificity to MW heating. It was able to reach a temperature of 110°C after 3 min of irradiation in a domestic oven (320 W). Mere 50 mg of $NaHSO_4 \cdot SiO_2$ catalyst to 0.01 moles of substrates was the most acceptable ratio in terms of efficiency and safety; a power level of 320 W was most suitable.

The conversion of 3,3-dimethyl-2,6-diaryl-piperidin-4-ones (*1–5*) into 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles (*11–15*) by this method was believed to be followed via the 3,3-dimethyl-2,6-diaryl-piperidin-4-one semicarbazones derivative **(6–10)**. In the first step, 3,3-dimethyl-2,6-diarylpiperidin-4-ones are converted to their respective semicarbazones and rapidly rearrange to give 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles in the second step. The attempt to isolate the respective semicarbazones from the reaction mixture was unsuccessful.

The formations of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles via the semicarbazones were confirmed by the same kind of reactions carried out using $NaHSO_4 \cdot SiO_2$ catalyst and 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones **(6–10)** and under microwave irradiation for 2–3 min. The products formed from the above two methods were found to be the same.

2.2. *Antibacterial and antifungal activity*

Novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles **11–15** were tested for their antibacterial activity (Table 2) *in vitro* minimum inhibitory concentration (MIC) in micrograms per milliliter against *Bacillus subtilis* and *Micrococcus luteus*, and the compounds were tested for their antifungal activity (Table 3) *in vitro* MIC in micrograms per milliliter



Scheme 1. One-pot synthesis of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4,-d]-1,2,3-thiadiazoles.

Table 1. Reaction and time yields of compounds 11–15.

	Microwave conditions		General conditions	
Compounds	Time (min)	Yield (%)	Time (min)	Yield (%)
11	5	90	60	45
12	4	85	50	51
13	4	88	45	55
14	5	90	60	62
15	4	94	45	60

Table 2. *In vitro* antibacterial activity (MIC) values for compounds 11–15.

	MIC	μg/mL
Compound	*B. subtilis*	*M. luteus*
11	100	100
12	50	100
13	50	50
14	6.25	12.5
15	6.25	6.25
Penicillin	25	25
Streptomycin	12.5	12.5

Table 3. *In vitro* antifungal activities (MIC) values for compounds 11–15.

	MIC (μg/mL)			
Compound	*A. niger*	*C. albicans*	*Candida-6*	*Candida-51*
11	100	–	200	–
12	100	50	50	50
13	50	100	100	–
14	25	6.25	100	50
15	12.5	12.5	6.25	12.5
Amphotericin-B	50	25	25	25

'–' No inhibition at 200 μg/mL.

against *Aspergillus niger, Candida albicans*, *Candida 6, and Candida 51*. Penicillin and Streptomycin were used as standards for bacterial studies; Amphotericin-B was used as a standard for fungal studies under analogous conditions. All the synthesized 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles **11–15** exerted a wide range of modest antibacterial and antifungal activities *in vitro* against the tested organisms, and the results are summarized in Tables 2 and 3.

3. Conclusion

In conclusion, we have developed an efficient, environmental-friendly,one-pot microwave-assisted synthesis of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thia-diazoles in good yields under short reaction time. A close examination of the *in vitro* antibacterial- and antifungal-activity profile in differently substituted novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles **11–15** against the tested bacterial strains *viz. B. subtilis* and *M. luteus* and the fungal strains *viz.*, *A. niger, C. albicans, Candida-6, Candida-51*, respectively, provides information that compounds having the electron-withdrawing functional group, namely chloro and fluoro, at the para position of the aryl moieties are determinant for the nature and extent of the activity of the synthesized compounds, which might have influences on their inhibiting mechanism of actions. The obtained results may be used as a key step for the building of novel chemical compounds with interesting antimicrobial profiles comparable with that of the standard drugs.

4. General remarks

4.1. *Microbiology*

4.1.1. *Materials*

All the bacterial strains, namely *B. subtilis* and *M. luteus*, and fungal strains, namely *A. niger, C. albicans, Candida-6 and Candida-51*, were obtained from the Faculty of Medicine, Annamalai University, Tamil Nadu.

4.1.2. In vitro *antibacterial and antifungal activity*

The *in vitro* activities of the compounds were tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media) for bacteria by a two-fold

serial dilution method (*29*). The respective hydrochlorides of the test compounds **23–27** were dissolved in water to obtain 1 mg mL^{-1} stock solution. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media) at 37 ± 1 °C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media) slant cultures were suspended in SDB. The colony forming units (cfu) of the seeded broth were determined by plating technique and adjusted in the range of 10^4–10^5 cfu/mL. The final inoculums size was 10^5 cfu/mL for an antibacterial assay and $1.1–1.5 \times 10^2$ cfu/mL for an antifungal assay. Testing was performed at pH 7.4 ± 0.2 for bacteria (NB) and at pH 5.6 for fungi (SDB). Exactly 0.4 mL of the solution of test compound was added to 1.6 mL of seeded broth to form the first dilution. About 1 mL of this was diluted with a further 1 mL of seeded broth to give the second dilution and so on till six such dilutions were obtained. A set of assay tubes containing only seeded broth was kept as control. The tubes were incubated in Biological Oxygen Demand (BOD) incubators at 37 ± 1 °C for bacteria and 72–96 h for fungi. MICs were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. Penicillin and streptomycin were used as standards for bacterial studies, and amphotericin-B was used as standards for fungal studies.

4.2. *Chemistry*

The reactions and purity of the products performing Thin Layer Chromatography (TLC) were assessed. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Nicolet Avatar 330 FT-IR spectrophotometer and noteworthy absorption values (per centimeter) alone were listed. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on Bruker AMX 400 NMR spectrometer using $CDCl_3$ as the solvent. The electron spray ionization positive MS spectra were recorded on a Bruker Daltonics LC–MS spectrometer. Satisfactory microanalysis was obtained on a Carlo Erba 1106 CHN analyzer. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230 V $\sim$ 50 Hz, 760 W) was used for the irradiation.

By adopting the previous literature (*30*), 3,3-dimethyl-2,6-diarylpiperidin-4-ones **(1–5)** and its semicarbazone derivatives **(6–10)** were prepared.

4.2.1. *General method of preparation of 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones* **6–10**

A mixture of 3,3-dimethyl-2,6-diarylpiperidin-4-one (0.01 mol), semicarbazide hydrochloride (0.01 mol), and sodium acetate (0.02 mol) in ethanol (40 mL) was refluxed on a steam bath for 30 min and concentrated to one-third of its original volume. After cooling, the mixture was poured over crushed ice. The solid product thus obtained was filtered off and recrystallized twice from ethanol to give 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones as crystalline solid.

4.2.2. *Typical procedure for the synthesis of 5,7-diphenyl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles* **11**

A mixture containing 0.01 mol of 3,3-dimethyl-2,6-diphenylpiperidin-4-one, 0.01 mol of semicarbazide, and 0.01 mol of thionyl chloride and $NaHSO_4 \cdot SiO_2$ (50 mg) was added in an alumina bath and mixed properly with the aid of glass rod (10 s) and then irradiated in a microwave oven for 5 min at 320 W (monitored by TLC). After the completion of the reaction, the reaction mixture was extracted with dichloromethane (3×5 mL). The catalyst and other solid wastes were removed by filtration. The combined organic layer was washed with water three times and then dried over anhydrous $MgSO_4$. The organic layer was concentrated

in vacuo to furnish the products that were purified by column chromatography using silica gel (100–200 mesh), with dichloromethane–petroleum ether (40–60) (5:1) as eluent. Yield: 90%; m.p. 127–28°C; MS: m/z 322, $M^{+\cdot}$; molecular formula: $C_{19}H_{19}N_3S$; elemental analysis: carbon 70.94_{found} (70.99_{cal}); hydrogen 5.94_{found} (5.96_{cal}); Nitrogen 13.03_{found} (13.07_{cal}); IR (KBr) (cm^{-1}): 3304, 3061, 3030, 2967, 2922, 2881, 2796, 1583, 684, 764, 705; ^{1}H NMR (δ ppm): 1.24 (s, 3H, equatorial CH_3 at C-4), 1.69 (s, 3H, axial CH_3 at C-4), 1.93 (s, 1H, H_6); 4.79 (s, 1H, H_5), 5.37 (s, 1H, H_7), 7.20–7.58 (m, 10H, H_{arom}); ^{13}C NMR (δ ppm): 26.3 CH_3 at C-4, 28.0 CH_3 at C-4, 37.4 C-4, 69.3 C-5, 73.8 C-7, 140.6, 142.7 *ipso*-C, 159.0 C-8, 170.6 C-9, 126.7–128.6$-C_{arom}$.

The compounds **12–15** were synthesized similarly.

4.2.3. *5,7-Bis(p-methylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles 12*

Irradiation reaction time = 4 min; yield: 85%; m.p. 143–44°C; MS: m/z 350, $M^{+\cdot}$; molecular formula: $C_{21}H_{23}N_3S$; elemental analysis: Carbon 72.15_{found} (72.17_{cal}); hydrogen 6.60_{found} (6.63_{cal}); nitrogen 11.98_{found} (12.02_{cal}); IR (KBr) (cm^{-1}): 3301, 3024, 2966, 2925, 2855, 1582, 817, 675; ^{1}H NMR (δ ppm): 1.20 (s, 3H, equatorial CH_3 at C-4), 1.70 (s, 3H, axial CH_3 at C-4), 2.26 (s, 1H, H_6); 2.32 (s, 6H, CH_3 at arom. ring), 4.84 (s, 1H, H_5), 5.40 (s, 1H, H_7), 7.14–7.25 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 21.0 CH_3 at arom. ring, 26.7 CH_3 at C-4, 28.3 CH_3 at C-4, 37.7 C-4, 68.3 C-5, 73.4 C-7, 134.7, 137.2, 141.3, 142.4 *ipso*-C, 158.4 C-8, 170.1 C-9, 127.2–129.3$-C_{arom}$.

4.2.4. *5,7-Bis(p-methoxylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles* **13**

Irradiation reaction time = 4 min; yield: 88%; m.p. 149–50°C; MS: m/z 382, $M^{+\cdot}$; Molecular formula: $C_{21}H_{23}N_3O_2S$; Elemental analysis: Carbon 66.08_{found} (66.12_{cal}); Hydrogen 6.04_{found} (6.08_{cal}); Nitrogen 10.99_{found} (11.01_{cal}); IR (KBr) (cm^{-1}):3313, 2957, 2924, 2921, 1576, 834, 678; ^{1}H NMR (δ ppm): 1.37 (s, 3H, equatorial CH_3 at C-4), 1.53 (s, 3H, axial CH_3 at C-4), 2.34 (s, 1H, H_6); 3.82 (s, 6H, OCH_3at arom. ring), 4.78 (s, 1H, H_5), 5.35 (s, 1H, H_7), 7.21-7.41 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 24.4 CH_3 at C-4, 25.4 CH_3 at C-4, 37.6 C-4, 55.1, 55.4 -OCH_3at arom. ring, 68.1 C-5, 73.3 C-7, 130.1, 131.8, 159.3, 159.6 *ipso*-C, 158.4 C-8, 170.3 C-9, 113.7-128.7 $-C_{arom}$.

4.2.5. *5,7-Bis(p-chlorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles* **14**

Irradiation reaction time = 5 min; yield: 90%; m.p. 161–62°C; MS: m/z 391, $M^{+\cdot}$; molecular formula: $C_{19}H_{17}Cl_2N_3S$; elemental analysis: carbon 58.43_{found} (58.46_{cal}); hydrogen 4.36_{found} (4.39_{cal}); nitrogen 10.73_{found} (10.77_{cal}); IR (KBr) (cm^{-1}): 3325, 3291, 2928, 2861, 1578, 834, 686; ^{1}H NMR (δ ppm): 1.21 (s, 3H, equatorial CH_3 at C-4), 1.70 (s, 3H, axial CH_3 at C-4), 2.14 (s, 1H, H_6), 4.47 (s, 1H, H_5), 5.08 (s, 1H, H_7), 7.18-7.47 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.2 CH_3 at C-4, 28.3 CH_3 at C-4, 37.3 C-4, 68.7 C-5, 73.0 C-7, 133.3, 136.6, 137.1, 138.7 *ipso*-C, 158.5 C-8, 170.7 C-9, 128.0–130.4 $-C_{arom}$.

4.2.6. *5,7-Bis(p-fluorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[4,3-d]-1,2,3-thiadiazoles* **15**

Irradiation reaction time = 4 min; yield: 94%; m.p. 165–66°C; MS: m/z 358, $M^{+\cdot}$; molecular formula: $C_{19}H_{17}F_2N_3S$; elemental analysis: carbon 63.82_{found} (63.85_{cal}); hydrogen 4.76_{found}

(4.79_{cal}); nitrogen 11.73_{found} (11.76_{cal}); IR (KBr) (cm^{-1}): 3318, 3297, 2924, 2857, 1574, 1211, 825, 681; ^1H NMR (δ ppm): 1.22 (s, 3H, equatorial CH_3 at C-4), 1.76 (s, 3H, axial CH_3 at C-4), 2.18 (s, 1H, H_6), 4.55 (s, 1H, H_5), 5.08 (s, 1H, H_7), 7.26-7.47 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.6 CH_3 at C-4, 28.5 CH_3 at C-4, 37.7 C-4, 69.0 C-5, 73.4 C-7, 134.2, 137.0, 138.6, 139.4 *ipso*-C, 159.1 C-8, 171.5 C-9, 128.5–131.4 $-C_{arom}$.

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References

(1) Rovira, C.; Veciana, J.; Santalo, N.; Tarres, J.; Cirujeda, J.; Molins, E. *J. Org. Chem.* **1994,** *59,* 3307.
(2) Stanetty, P.; Kremslehner, M. *Heterocycles* **1998,** *48,* 259.
(3) Britton, T.C.; Lobl, T.J.; Chidester, C.G. *J. Org. Chem*. **1984,** *49,* 4773.
(4) Stanetty, P.; Kremslehner, M.; Mullner, J. *J. Heterocycl. Chem*. **1996,** *33,* 1759.
(5) Lewis, G.S.; Nelson, P.H. *J. Med. Chem*. **1979,** *22,* 1214.
(6) Thomas, E.W.; Nishizawa, E.E.; Zimmermann, D.C.; Williams, J. *J. Med. Chem*. **1985,** *28,* 442.
(7) Hurd, C.D.; Mori, R.I. *J. Am. Chem. Soc*. **1955,** *77,* 5359.
(8) Thomas, E.W. In *Comprehensive Heterocyclic Chemistry*; Potts, K.T., Katritzky, A.R., Rees, C.W., Eds.; Pergamonn Press: London, 1984; Vol. 4B, p. 4476.
(9) Fujita, M.; Kobari, T.; Hiyama, T.; Konda, K. *Heterocycles* **1993,** *36,* 33.
(10) Byron, D.J.; Gray, G.W.; Wilson, R.C.J. *J. Chem. Soc. (C)* **1966,** *13,* 840.
(11) Tumkevicius, S.; Labanauskas, L.; Bacinskaite, V.; Brukstus, A.; Urbelis, G. *Tetrahedron Lett*. **2003,** *44,* 6635.
(12) Ghandi, H.; Anfoka, C. *Crop Prot.* **2000,** *19,* 401.
(13) Smeets, S.; Dehaen, W. *Tetrahedron Lett*. **1998,** *39,* 9841.
(14) El-Subbagh, H.I.; Abu-Zaid, S.M.; Mahran, M.A.; Badria, F.A.; Alofaid, A.M. *J. Med. Chem*. **2000,** *43,* 2915.
(15) Watson, A.A.; Fleet, G.W.J.; Asano, N.; Molyneux, R.J.; Nugh, R.J. *Phytochemistry* **2001,** *56,* 265.
(16) Ganellin, C.R.; Spickett, R.G. *J. Med. Chem*. **1965,** *8,* 619.
(17) Hagenbach, R.E.; Gysin, H. *Experimentia* **1952,** *8,* 184.
(18) Ileana, B.; Dobre, V.; Nicluescu-Duvaz, I. *J. Prakt. Chem*. **1985,** *327,* 667.
(19) Mokio, I.G.; Soldatenkov, A.T.; Federov, V.O.; Ageev, E.A.; Sergeeva, N.D.; Lin, S.; Stashenku, E.E.; Prostakov, N.S.; Andreeva, E.L. *Khim. Farm. Zh*. **1989,** *23,* 421.
(20) Dimmock, J.R.; Kumar, P. *Curr. Med. Chem*. **1997,** *4,* 1–22.
(21) Kubota, H.; Kakefuda, A.; Okamoto, Y.; Fujii, M.; Yamamoto, O.; Yamgiwa, Y.; Orita, M.; Ikeda, K.; Takenchi, M.; Shibanuma, T. *et al. Chem. Pharm. Bull.* **1998,** *46,* 1538.
(22) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J.; Govindaraju, R. *Arkivoc* **2006,** *13,* 130.
(23) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J.; Govindaraju, R.; Ezhilarasi, M.R. *Lett. Org. Chem*. **2006,** *3,* 484.
(24) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *Catalysis Commun*. **2005,** *6,* 753.
(25) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J.; Govindaraju, R. *J. Chem. Res*. **2005,** *5,* 299.
(26) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *Lett. Org. Chem*. **2005,** *2,* 444.
(27) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *J. Sulfur Chem.* **2007,** *28,* 383.
(28) Gopalakrishnan, M.; Sureshkumar, P.; Thanusu, J.; Kanagarajan, V.; Govindaraju, R.; Jayasri, G. *J. Enz. Inhib. Med. Chem*. **2007,** in press.
(29) Dhar, M.H.; Dhar, M.M.; Dhawan, B.N.; Mehrotra, B.N.; Ray, C. *Indian J. Exp. Biol.* **1968,** *6,* 232.
(30) Noller, C.R.; Baliah, V. *J. Am. Chem. Soc*. **1948,** *70,* 3853.