Facile Synthesis of Pyrimidine–Isoxazoline Hybrids in a [bmim][PF_6]–Water Biphasic System

Kushal Lanjewar,[a] Anjali Rahatgaonkar,*[a] Mukund Chorghade,[b] Binda Saraf[a]

[a] Chemistry Department, Institute of Science, Civil Lines, Nagpur 440001, MS, India
E-mail: anjali_rahatgaonkar@yahoo.com

[b] Chorghade Enterprises, 14 Carlson Circle, Natick, MA 01760-4205, USA

Received 25 March 2011; revised 5 May 2011

Abstract: The convenient synthesis of a library of pyrimidine–isoxazoline hybrids in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6])–water/potassium hydroxide at ambient temperature has been accomplished. The ionic liquid [bmim][PF_6], immiscible in water, can be easily recycled for reuse after separation of the products without any noticeable diminution in its activity. The protocol is rapid, the yields are good to excellent, and the method is facile.

Key words: pyrimidines, dihydroisoxazoles, ionic liquids, water, biphasic systems

Isoxazoles and their dihydro derivatives, isoxazolines, constitute an interesting heterocyclic family with diverse and defined therapeutic significance.[1] Such compounds exhibit analgesic, antimicrobial, antifungal, and anticancer activities. They are useful intermediates for the synthesis of a variety of bioactive natural products,[2] and they have also served as lead structures for new glutamic acid ligand receptor designs,[3] such as ionotropic (iGluRs) and metabotropic Glu receptors (mGluRs).

Several methods have been developed for the synthesis of isoxazolines or isoxazoles, such as the reaction of hydroxylamine with 1,3-dicarbonyl compounds,[4] α,β-unsaturated carbonyl compounds,[5] and α,β-unsaturated nitriles.[6] Previous reports reveal interesting methods for the synthesis of isoxazolines, e.g. 1,3-dipolar additions,[7] a photochemical reaction with nitrosonium tetrafluoroborate as catalyst,[8] solid-phase 1,3-dipolar cycloadditions,[9] syntheses of structurally diverse isoxazolines and isoxazoles in Magtrieve (CrO_2),[10] and ultrasound-promoted synthesis in water.[11] The synthesis of semisynthetic steroidal [16a,17a-*d*]-isoxazolines in the presence of chloramine-T in refluxing ethanol has been reported.[12] A tandem oximation–cyclization route to Δ^2-isoxazolines in ethanol–sodium hydroxide[13] has also been explored.

A wide variety of reagents, such as chlorine,[14] *N*-bromo-[15] and *N*-chlorosuccinimide,[16] sodium hypochlorite,[17] alkyl hypochlorites,[18] chloramine-T,[19] 1-chlorobenzotriazole,[20] benzyltrimethylammonium tetrachloroiodate,[21] and *N*-*tert*-butyl-*N*-chlorocyanamide,[22] have been used for the chloramination of aldoximes leading to isoxazoline synthesis. 1,3-Dipolar cycloadditions of nitrile oxides to various dipolarophiles[23] have been considerably accelerated in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4])[24] or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]).[25] The most convenient syntheses of isoxazolines have usually been in solvents such as dichloromethane, chloroform at 65 °C, methanol–sodium hydroxide at 80 °C, toluene at 80 °C, *N*,*N*-dimethylformamide, and ethanol–sodium hydroxide.

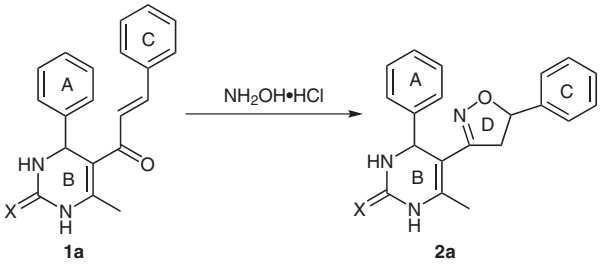
The hydrophobic ionic liquid [bmim][PF_6] is well known for its capability in various catalytic applications. In particular, hydrophobic media possessing hexafluorophosphate anions have a multitude of uses in different biochemical and chemical reactions.[26]

We have investigated the effect of different reaction conditions involving model hydrophobic ionic liquids, such as [bmim][PF_6], on the formation of isoxazolines, and we illustrate herein the extension of the use of [bmim][PF_6] to reactions of diversely substituted substrates. The possibility of adjusting solubility properties using [bmim][PF_6] combinations allows the systematic optimization of the productivity of the biphasic reaction.

We embarked on the synthesis of pyrimidine–isoxazoline hybrid compounds via the cyclocondensation of α,β-unsaturated carbonyl compounds with hydroxylamine hydrochloride. Several reaction conditions were explored in a diverse array of solvent systems. Few approaches have been used for the synthesis of heterocycles containing both isoxazoline and pyrimidine nuclei within a single molecular framework in ionic liquid–water biphasic systems. In our synthesis, described below, the model starting material 6-methyl-4-phenyl-5-(3-phenylacryloyl)-3,4-dihydropyrimidin-2(1*H*)-one was completely consumed after two hours when the reaction was conducted in a [bmim][PF_6]–water/potassium hydroxide biphasic solvent system; the corresponding product, 6-methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one, was formed in high yield. As previously reported in the literature, the reaction rate was sluggish in organic solvents. Our efforts at generating a representative library of isoxazolines using different concentrations of [bmim][PF_6] in biphasic solvent systems with addition of catalytic quantities of base are presented here, and our observations prompted us to explore the potential use of [bmim][PF_6]–water and potassium hydroxide.

SYNTHESIS 2011, No. 16, pp 2644–2650
Advanced online publication: 27.07.2011
DOI: 10.1055/s-0030-1260099; Art ID: M32611SS

Initially, 3,4-dihydropyrimidin-2(1*H*)-one **1a** was chosen as a model substrate in the reaction to give isoxazolines, forming 6-methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (**2a**) (Scheme 1). To optimize the reaction conditions, compound **1a** was subjected to the reaction with hydroxylamine hydrochloride in various solvents and over different periods to afford the corresponding pyrimidine–isoxazoline hybrid **2a** (Table 1).



Scheme 1 Synthesis of pyrimidine–isoxazoline hybrid **2a**

The reaction of **1a** in ethanol with a catalytic amount of potassium hydroxide at reflux was complete within 15 hours, giving **2a** in 65% isolated yield (Table 1, entry 1). The reaction time was carefully regulated to avoid the decomposition of the product and the formation of byproducts. It was observed that the reaction proceeded well on the addition of a small amount of water: the yield improved to 70% (entry 2). Thus, the efficiency of the reaction was markedly influenced by the nature of the solvent, i.e. by increasing the hydrophilicity of the reaction mixture. Further, the reaction in acetic acid and acetic acid–water at reflux for 15 hours diminished the yield (entries 3 and 4, respectively); however, using the latter solvent, the yield obtained was slightly higher than that achieved using the former solvent. The yield of **2a** was drastically reduced using *N*,*N*-dimethylformamide and *N*,*N*-dimethylformamide–water at reflux for 15 hours (entries 5 and 6, respectively); the latter reaction resulted in a 56% yield, indicating a preference for protic conditions.

Additionally, the reactions in the ionic liquids triethylammonium sulfate ($[Et_3NH][HSO_4]$ functions dually as solvent and catalyst), $[bmim][PF_6]$, $[bmim][PF_6]$–water, and $[bmim][PF_6]$–water/potassium hydroxide were monitored over various periods (entries 7–10, respectively); the reactions took place at ambient temperature in these ionic liquids. The use of $[bmim][PF_6]$–water/potassium hydroxide (entry 10) resulted in much higher reaction rates than those of the reactions performed in the other ionic liquid containing solvent systems (entries 7–9). Remarkably, it was observed that the reaction of substrate **1a** proceeded better in ionic liquids (entries 7–10) compared with that performed in common organic solvents (entries 1–6). The reaction in $[bmim][PF_6]$–water/potassium hydroxide unquestionably showed the highest levels of efficacy and atom economy compared with the reactions in the other solvents. In addition, the use of water as a secondary solvent in all the protic, aprotic, and ionic liquid systems improved the isolated yield. Using a catalytic amount of a base, a remarkable effect on the efficiency of the reaction in the solvent systems was also observed. Table 1 summarizes our results, clearly showing the superiority of an ionic liquid–water/potassium hydroxide biphasic system over an organic solvent–water system.

The course of the reaction was monitored by thin-layer chromatography (TLC), but we found that for all early experiments, TLC or high-performance liquid chromatography was not an optimal choice for the evaluation of yields or for a quantitative in-process assay. The viscous solution containing water and ionic liquids was not conducive to TLC and considerable streaking was discerned. We resorted to quenching the reactions and isolating the reported products. All elemental analyses were conducted on

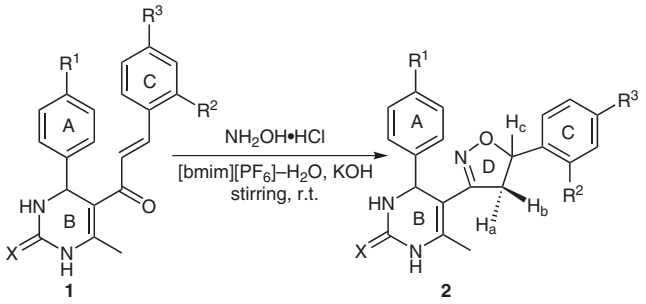
Table 1 Optimization of the Reaction Conditions for the Synthesis of 6-Methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (**2a**)

Entry	Solvent	Temp	Final isolated yield (%) at a given time					
			1 h	2 h	3 h	5 h	10 h	15 h
1	EtOH/KOH	reflux	10	22	29	40	55	65
2	EtOH–H_2O/KOH	reflux	13	21	34	51	66	70
3	AcOH	reflux	12	26	38	49	60	61
4	AcOH–H_2O	reflux	11	19	26	36	51	62
5	DMF	reflux	09	24	35	48	55	53
6	DMF–H_2O	reflux	10	26	38	46	50	56
7	$[Et_3NH][HSO_4]$	r.t.	15	32	50	75	76	77
8	$[bmim][PF_6]$	r.t.	29	48	68	87	88	88
9	$[bmim][PF_6]$–H_2O	r.t.	37	59	87	87	89	90
10	$[bmim][PF_6]$–H_2O/KOH	r.t.	50	93	93	93	93	93

isolated and purified compounds, and the yields were calculated based on the quantities of these final products.

We extended our investigation to the reactions of other substrates by introducing various substituents to rings A and C of the molecular framework of **1**; we also looked at related thione derivatives (Table 2).

Table 2 Synthesis of Substituted 5-(4,5-Dihydroisoxazol-3-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-ones and Related Thione Derivatives **2**



Entry	Product	R^1	R^2	R^3	X	Yield[a] (%)
1	**2a**	H	H	H	O	93
2	**2b**	H	H	OMe	O	85
3	**2c**	H	H	Cl	O	89
4	**2d**	OMe	H	H	O	87
5	**2e**	OMe	H	OMe	O	88
6	**2f**	OMe	H	Cl	O	92
7	**2g**	OH	H	H	O	82
8	**2h**	OH	H	OMe	O	84
9	**2i**	OH	Cl	H	O	88
10	**2j**	Cl	H	H	O	90
11	**2k**	Cl	H	OMe	O	89
12	**2l**	Cl	Cl	H	O	90
13	**2m**	H	H	H	S	89
14	**2n**	H	H	OMe	S	85
15	**2o**	H	Cl	H	S	90
16	**2p**	OMe	H	H	S	86
17	**2q**	OMe	H	OMe	S	85
18	**2r**	OMe	Cl	H	S	90

[a] Isolated yield.

The incorporation of electron-donating substituents at the *para*-position of ring A (R^1) resulted in a slight decrease in the yield (Table 2, entries 4 and 7 vs entry 1, and entry 16 vs entry 13). Electron-donating substituents at ring C (R^3) showed a very slight increase in reaction efficiency (Table 2, entry 5 vs entry 4 and entry 8 vs entry 7). Substrates with electron-withdrawing groups at the *para* positions of rings A (R^1) and C (R^3) (Table 2, entries 10, 11 and 12 vs entries 4 and 7, and entries 3 and 6 vs entry 2) displayed enhanced yields ranging from 90–92%. Thus, electron-withdrawing groups exert better influence than electron-donating substituents in enhancing the efficacy and yields of the reaction.

To verify the impact of the concentration of [bmim][PF_6] on the efficiency of the reaction, we gradually increased the quantity of [bmim][PF_6] from 1 to 15 millimoles while keeping the amount of water constant at 30 millimoles in reactions conducted at room temperature for two hours (Table 3). It was observed that as the concentration of [bmim][PF_6] in water increased, the efficiency of the reaction also increased. Variations in yield were observed; albeit minor, these prompted us to reproduce the procedure several times. We established that the variations in yield were not attributable to losses from workup. Beyond the use of 10 millimoles of [bmim][PF_6], the efficiency of the reaction decreased, suggesting that the nonpolar organic hydrophobic tail of the ionic liquid may interfere with the reaction mechanism.

Balanced hydrophobic–hydrophilic solvent interactions have been observed. Increased yields were noted on the addition of measured amounts of water to all solvent systems (*vide supra*), suggesting that an environment of polar or protic solvents is more conducive to the reaction.

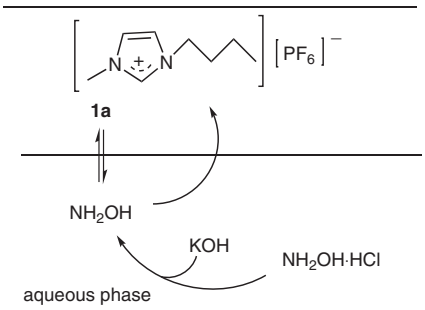
Table 3 Effect of Varying the Concentration of the Ionic Liquid [bmim][PF_6] in Water/KOH for the Synthesis of 6-Methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (**2a**)[a]

Entry	[bmim][PF_6] (mmol)	Yield (%)
1	1	81
2	3	85
3	7	89
4	10	93
5	13	90
6	15	87

[a] With H_2O (30 mmol) and KOH (1 mmol) at r.t. for 2 h.

Interestingly, the ionic liquid–water biphasic system [bmim][PF_6]–water/potassium hydroxide proved to be exceptionally effective at enhancing the efficiency of the reaction. The ionic liquid [bmim][PF_6] is used in a biphasic system as a substrate reservoir for substrates that are poorly soluble in water–organic solvent mixtures. A plausible explanation of the reaction mechanism in the ionic liquid–water biphasic system is as follows: The ionic liquid [bmim][PF_6] is hydrophobic and immiscible with water. One of the reactants, the pyrimidinone, e.g. **1a**, is hydrophobic while hydroxylamine hydrochloride is hydrophilic in nature. The different solvation affinities of these two reactants retard the reaction. The [bmim][PF_6]–water/potas-

sium hydroxide solvent system provides a platform for the nonpolar organic counterpart [bmim]$^+$ to easily make **1a** soluble; $[PF_6]^-$ and the water/potassium hydroxide counterpart make hydroxylamine hydrochloride soluble. The free hydroxylamine, produced in situ in the aqueous phase by the reaction of hydroxylamine hydrochloride and potassium hydroxide, is transported to the ionic liquid phase where the reaction may occur at the junction of the two immiscible solvents (Scheme 2). This suggests that the ionic liquid biphasic system effectively delivers the substrates at the interface of two immiscible liquids.



Scheme 2 A plausible reaction mechanism in an ionic liquid–water biphasic system

For each reaction, we have optimized the extraction and isolation of the resulting product in the ionic liquid phase using various solvents, such as diethyl ether, dichloromethane, ethyl acetate, and *n*-hexane; the best results were obtained with diethyl ether and this was the solvent of choice for further experiments. Inorganic salts, formed as byproducts, dissolved in water. The separated ionic liquid was flushed out with water and reused directly without further purification and without great diminution of the yields in up to 10 reaction cycles; however, there was a noticeable drop in yield after the 10th cycle, suggesting that the catalyst may have become contaminated, degraded, or exhausted (Table 4). Our protocol has the merit of being environmentally benign and a simple operation, involving convenient workup, a short reaction time, and proceeding in good to excellent yields.

Table 4 Effect of the Reuse of the Ionic Liquid [bmim][PF_6] on the Formation of 6-Methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (**2a**)

Entry	Ionic liquid recycling	Yield (%)
1	0	93
2	1	92
3	2	92
4	3	91
5	4	91
6	5	90
7	6	89
8	7	87
9	8	85
10	9	81
11	10	75
12	11	67
13	12	55

Contributing to the elucidation of the structures of compounds **2a**–**r** (see Table 2), their infrared spectra showed a peak at 519–526 cm^{-1} owing to C=N stretching of the isoxazoline ring and peaks at 828–835 and 968–974 cm^{-1} because of N–O and C–O–N stretching, respectively, of the isoxazoline ring. Furthermore, the ^{1}H NMR spectra of compounds **2a**–**r** showed a singlet of three protons at δ = 2.04–2.20 ppm owing to the $ArCH_3$ protons. In the isoxazoline ring there are three types of hydrogen, one attached to the C-5 carbon, i.e. H_c, and two at C-4. The two hydrogens attached at the 4-position are *cis* and *trans* H_a and H_b, respectively. The ^{1}H NMR spectra for model compound **2a** showed a doublet at δ = 2.59–2.61 ppm owing to the H_a proton. Proton H_b coupled with both H_a and H_c to give a double doublet at δ = 3.19–3.22 ppm. The doublet at δ = 5.09–5.13 ppm owing to the H_c proton confirms the structure of the isoxazoline ring. A signal owing to the proton in a hydroxy group appeared at δ = 10.50–10.53 ppm in the spectra of compounds **2g**–**i**. In addition, the three protons of the methoxy group in compounds **2b**, **2d**–**f**, **2h**, **2k**, **2n**, and **2p**–**r** resonated as a singlet at δ = 3.78–3.87 ppm. The ^{13}C NMR spectra also support the structures of the products; signals at δ = 25.4–28.0, 72.0–82.2, and 155.6–161.2 ppm indicated the presence of an isoxazoline ring. Satisfactory elemental analyses were obtained for compounds **2a**–**r**, and the mass spectral data also lent credence to the assigned structures.

In conclusion, [bmim][PF_6]–water/potassium hydroxide proved to be an exceptionally efficient biphasic solvent system for the synthesis of pyrimidine–isoxazoline hybrids at ambient temperature within two hours. The protocol has the merit of being environmentally friendly and a simple operation, involving convenient workup, a short reaction time, and resulting in good to excellent yields. The ionic liquid [bmim][PF_6] can be reused in up to 10 reaction cycles, but after this the loss of its activity has been observed. The reaction is influenced by aqueous potassium hydroxide. The ionic liquid [bmim][PF_6] stabilizes the hydrophobic reactant, and water stabilizes hydroxylamine hydrochloride; the reaction presumably occurs at the junction of the two immiscible phases.

All solvents were distilled prior to use. Thin-layer chromatography was performed on silica gel G (Qualigen). Melting points were determined by the open capillary method and are uncorrected. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 400 NMR spectrometer and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury YH-300 spectrometer. Chemical shifts are reported using TMS as an internal standard. The IR spectra were obtained on a Shimadzu FT-IR spectrophotometer using KBr discs.

Mass spectra were recorded using a Shimadzu gas chromatograph. Elemental analyses were performed on a Perkin-Elmer 2400 instrument.

6-Methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (2a); Typical Procedure

A mixture of 6-methyl-4-phenyl-5-(3-phenylacryloyl)-3,4-dihydropyrimidin-2(1*H*)-one (**1a**) (0.95 g, 3 mmol), hydroxylamine hydrochloride (0.28 g, 4 mmol), and KOH (0.056 g, 1 mmol) was introduced to a vigorously stirred mixture of the [bmim][PF_6] (2.84 g, 2 mL, 10 mmol) and H_2O (0.54 g, 30 mmol) biphasic solvent system at r.t., and stirring was continued for 2 h. The course of reaction was monitored by TLC. After completion, the reaction was quenched with H_2O (5 mL), and the immiscible ionic liquid [bmim][PF_6] layer was separated from the aqueous phase and extracted with Et_2O (3 × 10 mL). The organic layer was dried (anhyd Na_2SO_4) and then concentrated in vacuo to afford the pure product as a yellow solid. Yield: 0.92 g (93%); mp 148 °C.

The recycled ionic liquid was reused in the next reaction without any noticeable effect on the results.

IR (KBr): 522, 831, 970 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3 H, $ArCH_3$), 2.59–2.61 (d, *J* = 7.4 Hz, 1 H, H_a), 3.19–3.22 (dd, *J* = 8.8, 2.3 Hz, 1 H, H_b), 4.98 (s, 1 H, CH), 5.09–5.13 (d, *J* = 10.3 Hz, 1 H, H_c), 6.68 (s, 1 H, NH), 6.82–7.48 (m, 10 H, ArH), 7.96 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 27.0, 46.8, 82.0, 110.2, 126.2, 127.0, 127.9, 129.6, 140.2, 143.8, 144.4, 150.8, 155.6.

GC-MS (70 eV): *m*/*z* = 333 [M^+].

Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.07; H, 5.72; N, 12.61. Found: C, 72.01; H, 5.62; N, 12.55.

5-[5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (2b)

Yield: 930 mg (85%); yellow solid; mp 112 °C.

IR (KBr): 521, 833, 971 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.17 (s, 3 H, $ArCH_3$), 2.57–2.59 (d, *J* = 8.5 Hz, 1 H, H_a), 3.22–3.29 (dd, *J* = 8.4, 6.4 Hz, 1 H, H_b), 3.82 (s, 3 H, OCH_3), 4.96 (s, 1 H, CH), 5.08–5.10 (d, *J* = 10.3 Hz, 1 H, H_c), 6.42 (s, 1 H, NH), 6.62–7.44 (m, 9 H, ArH), 8.00 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2, 26.8, 46.4, 55.8, 82.0, 109.4, 113.6, 126.4, 126.8, 128.0, 134.0, 143.8, 144.2, 150.6, 155.2, 161.2.

GC-MS (70 eV): *m*/*z* = 363 [M^+].

Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.33; H, 5.64; N, 11.43.

5-[5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (2c)

Yield: 980 mg (89%); yellow solid; mp 150 °C.

IR (KBr): 520, 832, 969 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3 H, $ArCH_3$), 2.62–2.64 (d, *J* = 8.6 Hz, 1 H, H_a), 3.22–3.29 (dd, *J* = 8.0, 7.4 Hz, 1 H, H_b), 4.90 (s, 1 H, CH), 5.05–5.08 (d, *J* = 11.6 Hz, 1 H, H_c), 6.71 (s, 1 H, NH), 7.00–7.44 (m, 9 H, ArH), 7.86 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 26.8, 47.4, 80.2, 108.2, 126.0, 126.6, 128.0, 129.2, 132.4, 137.4, 143.8, 144.0, 151.0, 155.2.

GC-MS (70 eV): *m*/*z* = 367 [M^+].

Anal. Calcd. for $C_{20}H_{18}N_3O_2Cl$: C, 65.39; H, 4.90; N, 11.44. Found: C, 65.29; H, 4.79; N, 11.42.

4-(4-Methoxyphenyl)-6-methyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (2d)

Yield: 950 mg (87%); yellow solid; mp 173 °C.

IR (KBr): 521, 830, 973 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.20 (s, 3 H, $ArCH_3$), 2.61–2.63 (d, *J* = 8.2 Hz, 1 H, H_a), 3.23–3.28 (dd, *J* = 9.7, 8.6 Hz, 1 H, H_b), 3.78 (s, 3 H, OCH_3), 4.91 (s, 1 H, CH), 5.06–5.09 (d, *J* = 12.6 Hz, 1 H, H_c), 6.45 (s, 1 H, NH), 7.10–7.50 (m, 9 H, ArH), 7.68 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 27.0, 46.4, 55.8, 82.0, 109.6, 113.8, 127.0, 127.4, 128.2, 129.6, 134.0, 141.4, 144.2, 150.8, 155.0, 159.6.

GC-MS (70 eV): *m*/*z* = 363 [M^+].

Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.42; H, 5.78; N, 11.57. Found: C, 69.38; H, 5.67; N, 11.49.

4-(4-Methoxyphenyl)-5-[5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2e)

Yield: 1040 mg (88%); yellow solid; mp 160 °C.

IR (KBr): 519, 829, 972 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.10 (s, 3 H, $ArCH_3$), 2.63–2.65 (d, *J* = 8.4 Hz, 1 H, H_a), 3.23–3.29 (dd, *J* = 9.7, 8.6 Hz, 1 H, H_b), 3.79 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.91 (s, 1 H, CH), 5.07–5.09 (d, *J* = 11.0 Hz, 1 H, H_c), 7.08 (s, 1 H, NH), 7.30–7.51 (m, 8 H, ArH), 7.68 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0, 26.2, 47.2, 55.8, 81.0, 109.4, 113.8, 114.0, 127.2, 132.0, 133.8, 144.0, 150.6, 154.8, 159.4, 159.6.

GC-MS (70 eV): *m*/*z* = 393 [M^+].

Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.17; H, 5.85; N, 10.68. Found: C, 66.99; H, 5.82; N, 10.61.

5-[5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-yl]-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2f)

Yield: 1100 mg (92%); yellow solid; mp 148 °C.

IR (KBr): 524, 830, 968 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.04 (s, 3 H, $ArCH_3$), 2.60–2.62 (d, *J* = 7.0 Hz, 1 H, H_a), 3.26–3.29 (dd, *J* = 7.2, 7.2 Hz, 1 H, H_b), 3.82 (s, 3 H, OCH_3), 4.88 (s, 1 H, CH), 5.11–5.14 (d, *J* = 11.1 Hz, 1 H, H_c), 7.02 (s, 1 H, NH), 7.10–7.44 (m, 8 H, ArH), 7.56 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 25.8, 47.2, 55.8, 81.9, 108.8, 113.6, 127.0, 128.0, 133.8, 134.0, 138.6, 144.2, 150.2, 154.0, 159.2.

GC-MS (70 eV): *m*/*z* = 397 [M^+].

Anal. Calcd for $C_{21}H_{20}N_3O_3Cl$: C, 63.47; H, 5.03; N, 10.57. Found: C, 63.32; H, 4.91; N, 10.43.

4-(4-Hydroxyphenyl)-6-methyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (2g)

Yield: 860 mg (82%); yellow solid; mp 172 °C.

IR (KBr): 520, 828, 968 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, $ArCH_3$), 2.51–2.53 (d, *J* = 8.56 Hz, 1 H, H_a), 3.11–3.16 (dd, *J* = 7.4, 8.6 Hz, 1 H, H_b), 4.80 (s, 1 H, CH), 5.21–5.23 (d, *J* = 10.96 Hz, 1 H, H_c), 6.68 (s, 1 H, NH), 7.10–7.68 (m, 9 H, ArH), 7.70 (s, 1 H, NH), 10.50 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 27.8, 47.0, 81.8, 108.0, 115.8, 126.8, 127.0, 127.4, 128.8, 130.6, 140.0, 144.0, 150.6, 155.0, 155.8.

GC-MS (70 eV): *m*/*z* = 349 [M^+].

Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.76; H, 5.44; N, 12.03. Found: C, 68.61; H, 5.29; N, 11.96.

4-(4-Hydroxyphenyl)-5-[5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2h)
Yield: 960 mg (84%); yellow solid; mp 180 °C.

IR (KBr): 525, 833, 973 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, $ArCH_3$), 2.59–2.61 (d, *J* = 8.6 Hz, 1 H, H_a), 3.19–3.22 (dd, *J* = 8.2, 7.0 Hz, 1 H, H_b), 3.85 (s, 3 H, OCH_3), 4.77 (s, 1 H, CH), 5.22–5.25 (d, *J* = 10.6 Hz, 1 H, H_c), 7.12 (s, 1 H, NH), 7.25–7.70 (m, 8 H, ArH), 7.75 (s, 1 H, NH), 10.53 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 27.8, 47.6, 55.9, 81.0, 108.2, 114.0, 115.2, 128.4, 129.0, 132.6, 135.8, 144.0, 150.6, 155.0, 155.8, 159.8.

GC-MS (70 eV): *m*/*z* = 379 [M^+].

Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.49; H, 5.54; N, 11.08. Found: C, 66.45; H, 5.42; N, 11.03.

5-[5-(2-Chlorophenyl)-4,5-dihydroisoxazol-3-yl]-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2i)
Yield: 1010 mg (88%); yellow solid; mp 125 °C.

IR (KBr): 521, 835, 969 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, $ArCH_3$), 2.51–2.53 (d, *J* = 9.0 Hz, 1 H, H_a), 3.12–3.17 (dd, *J* = 7.4, 8.6 Hz, 1 H, H_b), 4.80 (s, 1 H, CH), 5.20–5.23 (d, *J* = 11.4 Hz, 1 H, H_c), 6.68 (s, 1 H, NH), 7.10–7.68 (m, 8 H, ArH), 7.70 (s, 1 H, NH), 10.50 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 25.8, 47.2, 73.0, 108.8, 115.4, 126.4, 127.6, 128.8, 132.0, 134.0, 136.4, 143.8, 150.6, 155.2, 155.8.

GC-MS (70 eV): *m*/*z* = 383 [M^+].

Anal. Calcd for $C_{20}H_{18}N_3O_3Cl$: C, 62.66; H, 4.70; N, 10.96. Found: C, 62.55; H, 4.65; N, 10.89.

4-(4-Chlorophenyl)-6-methyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (2j)
Yield: 990 mg (90%); yellow solid; mp 178 °C.

IR (KBr): 524, 832, 972 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.09 (s, 3 H, $ArCH_3$), 2.71–2.73 (d, *J* = 8.5 Hz, 1 H, H_a), 3.19–3.24 (dd, *J* = 8.4, 8.4 Hz, 1 H, H_b), 4.97 (s, 1 H, CH), 5.05–5.08 (d, *J* = 11.5 Hz, 1 H, H_c), 6.95 (s, 1 H, NH), 7.05–7.41 (m, 9 H, ArH), 7.58 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 25.8, 47.8, 82.0, 109.0, 126.8, 127.2, 129.0, 129.4, 129.8, 132.0, 140.0, 141.4, 145.0, 150.6, 155.2.

GC-MS (70 eV): *m*/*z* = 367 [M^+].

Anal. Calcd for $C_{20}H_{18}N_3O_2Cl$: C, 65.39; H, 4.90; N, 11.44. Found: C, 65.32; H, 4.87; N, 11.36.

4-(4-Chlorophenyl)-5-[5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2k)
Yield: 1060 mg (89%); yellow solid; mp 168 °C.

IR (KBr): 519, 829, 968 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3 H, $ArCH_3$), 2.63–2.65 (d, *J* = 8.6 Hz, 1 H, H_a), 3.23–3.29 (dd, *J* = 8.0, 7.4 Hz, 1 H, H_b), 3.87 (s, 3 H, OCH_3), 4.90 (s, 1 H, CH), 5.06–5.09 (d, *J* = 11.1 Hz, 1 H, H_c), 6.78 (s, 1 H, NH), 7.07–7.39 (m, 8 H, ArH), 7.86 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 25.8, 47.2, 57.0, 81.9, 108.8, 115.8, 127.8, 128.0, 128.4, 128.8, 132.0, 134.4, 141.8, 145.6, 150.6, 155.2, 160.6.

GC-MS (70 eV): *m*/*z* = 397 [M^+].

Anal. Calcd for $C_{21}H_{20}N_3O_3Cl$: C, 63.47; H, 5.03; N, 10.58. Found: C, 63.38; H, 5.01; N, 10.45.

4-(4-Chlorophenyl)-5-[5-(2-chlorophenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (2l)
Yield: 1080 mg (90%); yellow solid; mp 158 °C.

IR (KBr): 523, 834, 972 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3 H, $ArCH_3$), 2.62–2.64 (d, *J* = 7.8 Hz, 1 H, H_a), 3.23–3.27 (dd, *J* = 7.9, 6.3 Hz, 1 H, H_b), 4.91 (s, 1 H, CH), 5.07–5.10 (d, *J* = 11.5 Hz, 1 H, H_c), 7.03 (s, 1 H, NH), 7.12–7.44 (m, 8 H, ArH), 7.55 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 25.6, 48.0, 74.6, 108.8, 127.0, 128.8, 129.8, 130.2, 132.0, 136.6, 142.0, 145.8, 150.4, 156.2.

GC-MS (70 eV): *m*/*z* = 401 [M^+].

Anal. Calcd for $C_{20}H_{17}N_3O_2Cl_2$: C, 59.85; H, 4.23; N, 10.47. Found: C, 59.74; H, 4.20; N, 10.36.

6-Methyl-4-phenyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)-thione (2m)
Yield: 930 mg (89%); yellow solid; mp 150 °C.

IR (KBr): 522, 833, 971 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.12 (s, 3 H, $ArCH_3$), 2.61–2.63 (d, *J* = 8.2 Hz, 1 H, H_a), 3.20–3.23 (dd, *J* = 4.9, 3.5 Hz, 1 H, H_b), 3.56 (s, 1 H, NH), 4.19 (s, 1 H, NH), 4.97 (s, 1 H, CH), 5.07–5.10 (d, *J* = 10.7 Hz, 1 H, H_c), 6.83–7.48 (m, 10 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 26.4, 52.8, 82.2, 107.8, 126.0, 126.4, 127.2, 129.4, 130.0, 141.8, 144.2, 155.8, 158.0, 181.0.

GC-MS (70 eV): *m*/*z* = 349 [M^+].

Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.77; H, 5.44; N, 12.03. Found: C, 68.65; H, 5.36; N, 11.91.

5-[5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (2n)
Yield: 970 mg (85%); yellow solid; mp 138 °C.

IR (KBr): 525, 831, 970 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.17 (s, 3 H, $ArCH_3$), 2.57–2.59 (d, *J* = 8.6 Hz, 1 H, H_a), 3.24–3.29 (dd, *J* = 8.4, 7.2 Hz, 1 H, H_b), 3.55 (s, 1 H, NH), 3.82 (s, 3 H, OCH_3), 4.29 (s, 1 H, NH), 4.96 (s, 1 H, CH), 5.08–5.11 (d, *J* = 15.08 Hz, 1 H, H_c), 6.78–7.44 (m, 9 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 26.4, 52.0, 55.8, 82.0, 108.0, 115.2, 126.4, 127.2, 128.2, 129.0, 134.2, 144.4, 155.8, 156.8, 159.0, 181.2.

GC-MS (70 eV): *m*/*z* = 379 [M^+].

Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 66.49; H, 5.54; N, 11.08. Found: C, 66.25; H, 5.41; N, 10.95.

5-[5-(2-Chlorophenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (2o)
Yield: 1030 mg (90%); yellow solid; mp 168 °C.

IR (KBr): 522, 830, 974 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3 H, $ArCH_3$), 2.60–2.62 (d, *J* = 8.2 Hz, 1 H, H_a), 3.23–3.29 (dd, *J* = 8.0, 7.4 Hz, 1 H, H_b), 3.54 (s, 1 H, NH), 4.20 (s, 1 H, NH), 4.90 (s, 1 H, CH), 5.06–5.09 (d, *J* = 11.5 Hz, 1 H, H_c), 7.00–7.44 (m, 9 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 26.8, 52.6, 72.0, 108.4, 126.6, 127.8, 128.6, 129.8, 133.4, 137.8, 143.6, 155.6, 160.0, 181.2.

GC-MS (70 eV): *m*/*z* = 383 [M^+].

Anal. Calcd for $C_{20}H_{18}N_3OSCl$: C, 62.66; H, 4.70; N, 10.97. Found: C, 62.53; H, 4.57; N, 10.88.

4-(4-Methoxyphenyl)-6-methyl-5-(5-phenyl-4,5-dihydroisoxazol-3-yl)-3,4-dihydropyrimidine-2(1*H*)-thione (2p)
Yield: 980 mg (86%); yellow solid; mp 160 °C.

IR (KBr): 526, 831, 972 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.17 (s, 3 H, $ArCH_3$), 2.23–2.25 (d, *J* = 5.8 Hz, 1 H, H_a,), 3.23–3.29 (dd, *J* = 8.4, 6.4 Hz, 1 H, H_b), 3.55 (s, 1 H, NH), 3.82 (s, 3 H, OCH_3), 4.35 (s, 1 H, NH), 4.96 (s, 1 H, CH), 5.07–5.10 (d, *J* = 11.0 Hz, 1 H, H_c), 6.87–7.44 (m, 9 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 28.0, 53.0, 55.8, 82.2, 107.6, 115.0, 127.8, 129.8, 130.6, 135.8, 140.8, 156.0, 158.0, 159.4, 181.2.

GC-MS (70 eV): *m*/*z* = 379 [M^+].

Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 66.49; H, 5.54; N, 11.08. Found: C, 66.29; H, 5.34; N, 10.88.

4-(4-Methoxyphenyl)-5-[5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl]-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (2q)
Yield: 1040 mg (85%); yellow solid; mp 165 °C.

IR (KBr): 521, 829, 970 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.10 (s, 3 H, $ArCH_3$), 2.62–2.64 (d, *J* = 9.7 Hz, 1 H, H_a), 3.23–3.29 (dd, *J* = 9.7, 8.6 Hz, 1 H, H_b), 3.37 (s, 1 H, NH), 3.78 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.31 (s, 1 H, NH), 4.91 (s, 1 H, CH), 5.07–5.09 (d, *J* = 11.0 Hz, 1 H, H_c), 7.29–7.51 (m, 8 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 27.8, 52.6, 55.8, 56.0, 82.2, 108.0, 115.7, 115.9, 129.4, 133.6, 135.9, 155.0, 157.8, 158.4, 159.6, 181.0.

GC-MS (70 eV): *m*/*z* = 409 [M^+].

Anal. Calcd for $C_{22}H_{23}N_3O_3S$: C, 64.55; H, 5.62; N, 10.27. Found: C, 64.41; H, 5.48; N, 10.05.

5-[5-(2-Chlorophenyl)-4,5-dihydroisoxazol-3-yl]-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-thione (2r)
Yield: 1120 mg (90%); yellow solid; mp 184 °C.

IR (KBr): 525, 833, 968 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.04 (s, 3 H, $ArCH_3$), 2.60–2.62 (d, *J* = 8.2 Hz, 1 H, H_a), 3.26–3.29 (dd, *J* = 6.6, 5.6 Hz, 1 H, H_b), 3.49 (s, 1 H, NH), 3.78 (s, 3 H, OCH_3), 4.29 (s, 1 H, NH), 4.88 (s, 1 H, CH), 5.13–5.16 (d, *J* = 11.1 Hz, 1 H, H_c), 7.10–7.44 (m, 8 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 25.4, 52.6, 55.8, 73.0, 108.4, 115.6, 127.8, 128.0, 129.0, 129.8, 133.9, 136.0, 137.6, 154.6, 155.8, 159.8, 180.8.

GC-MS (70 eV): *m*/*z* = 413 [M^+].

Anal. Calcd for $C_{21}H_{20}N_3O_2SCl$: C, 61.01; H, 4.84; N, 10.17. Found: C, 60.89; H, 4.78; N, 10.09.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

The authors wish to express their gratitude to the Department of Pharmacy, Nagpur, for IR spectroscopic analysis, the Sophisticated Analytical Instrumentation Facility (SAIF), Chandigarh, for ^1H NMR spectroscopic analysis, and the University of Pune for ^{13}C NMR spectroscopic and mass analysis.

References

(1) Gaonkar, S. L.; Lokanatha Rai, K. M.; Prabhuswamy, B. *Med. Chem. Res.* **2007**, *15*, 407.
(2) (a) Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991. (b) Haino, T.; Tanaka, M.; Ikeda, K.; Kubo, K.; Mori, A.; Fukazawa, Y. *Tetrahedron Lett.* **2004**, *45*, 2277.
(3) (a) Kromann, H.; Slok, F. A.; Stensbol, T. B.; Brauner-Osborne, H.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2002**, *45*, 988. (b) Conti, P.; De Amici, M.; Roda, G.; Vistoli, G.; Stensbol, T. B.; Brauner-Osborne, H.; Madsen, U.; Toma, L.; De Micheli, C. *Tetrahedron* **2003**, *59*, 1443.
(4) Hansen, T. V.; Wu, P.; Fokin, V. V. *J. Org. Chem.* **2005**, *70*, 7761.
(5) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203.
(6) Vicentini, C. B.; Verones, A. C.; Poli, T.; Guameri, M.; Gioni, P.; Ferreti, V. *J. Heterocycl. Chem.* **1990**, *27*, 1481.
(7) Higashida, S.; Nakashima, H.; Tohda, Y.; Tani, K.; Nishiwaki, N.; Ariga, M. *Heterocycles* **1992**, *34*, 1511.
(8) Mizuno, K.; Ichinose, N.; Tamai, T.; Otsuja, Y. *J. Org. Chem.* **1992**, *57*, 4669.
(9) Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. *Tetrahedron Lett.* **1998**, *39*, 2447.
(10) Bhosale, S.; Kurhade, S.; Prasad, U. V.; Palle, V. P.; Bhuniya, D. *Tetrahedron Lett.* **2009**, *50*, 3948.
(11) Martins, M. A. P.; Pereira, C. M. P.; Cunico, W.; Moura, S.; Rosa, F. A.; Peres, R. L.; Machado, P.; Zanatta, N.; Bonacorso, H. G. *Ultrason. Sonochem.* **2006**, *13*, 364.
(12) Chowdhury, P.; Das, A. M.; Goswami, P. *Steroids* **2005**, *70*, 494.
(13) Norman, A. L.; Shurrush, K. A.; Calleroz, A. T.; Mosher, M. D. *Tetrahedron Lett.* **2007**, *48*, 6849.
(14) (a) Eibler, E.; Kasbauer, J.; Pohl, H.; Sauer, J. *Tetrahedron Lett.* **1987**, *28*, 1097. (b) Corbett, D. F. *J. Chem. Soc., Perkin Trans. 1* **1986**, 421.
(15) Armstrong, S. K.; Collington, E. W.; Knight, J. G.; Naylorb, A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1433.
(16) (a) Liu, K. C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916. (b) Gi, H. J.; Xiang, Y.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, *62*, 88.
(17) Lee, G. A. *Synthesis* **1982**, 508.
(18) Ye, Y.; Zheng, Y.; Xu, G. Y.; Liu, L. Z. *Heteroat. Chem.* **2003**, *14*, 254.
(19) Hassner, A.; Lokanatha Rai, K. M. *Synthesis* **1989**, 57.
(20) Kim, J.; Ryu, E. *Synth. Commun.* **1990**, *20*, 1373.
(21) Kanemasa, S.; Matsuda, H.; Kamimurac, A.; Kakinamid, T. *Tetrahedron* **2000**, *56*, 1057.
(22) Kumar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2006**, *47*, 1457.
(23) Seregin, I. V.; Ovchinnikov, I. V.; Makhova, N. N.; Lyubetsky, D. V.; Lyssenko, K. A. *Mendeleev Commun.* **2003**, *13*, 230.
(24) Armstrong, W.; He, L.; Liu, Y. S. *Anal. Chem.* **1999**, *71*, 3873.
(25) Suarez, P. A.; Dullius, J. E. L.; Einloft, S.; DeSouza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217.
(26) Manthiriyappan, S.; Lee, C. K. *J. Mol. Catal. B: Enzym.* **2009**, *60*, 1.