SYNTHESIS OF SOME NOVEL ISOXAZOLYL-SPIRO-[3*H*-INDOLE-3,2'-THIAZOLIDINE]-2,4'-(1*H*)-DIONES, [3*H*-INDOLE-3,4'-AZETIDINE]-2,2'-(1*H*)-DIONES AND [3*H*-INDOLE-3,5'-3'-PHENYL-1',2',4'-OXADIAZOLINE]-2(1*H*)-ONES

E. Rajanarendar*, G. Mohan, P. Ramesh and E. Kalyan Rao
Department of Chemistry, Kakatiya University, Warangal – 506 009, India.
E-mail : eligeti_rajan@yahoo.co.in

Abstract : Condensation of 4-amino-3-melthyl-5-styrylisoxazoles **1** with different isatins **2** gives 3-(3-methyl-5-styryl-4-isoxazolylimino)-2-indolinones **3**. Cyclocondensation of **3** with mercaptoacetic acid and chloroacetyl chloride affords spiro thiazolidinones **4** and spiroazetidinones **5** respectively, while cycloaddition of **3** with benzo nitrileoxide leads to spiro 1,2,4-oxadiazolines **6**. The structures of the compounds **3-6** have been established on the basis of their elemental analyses and spectral (IR, ^{1}H NMR and mass) data.

Introduction

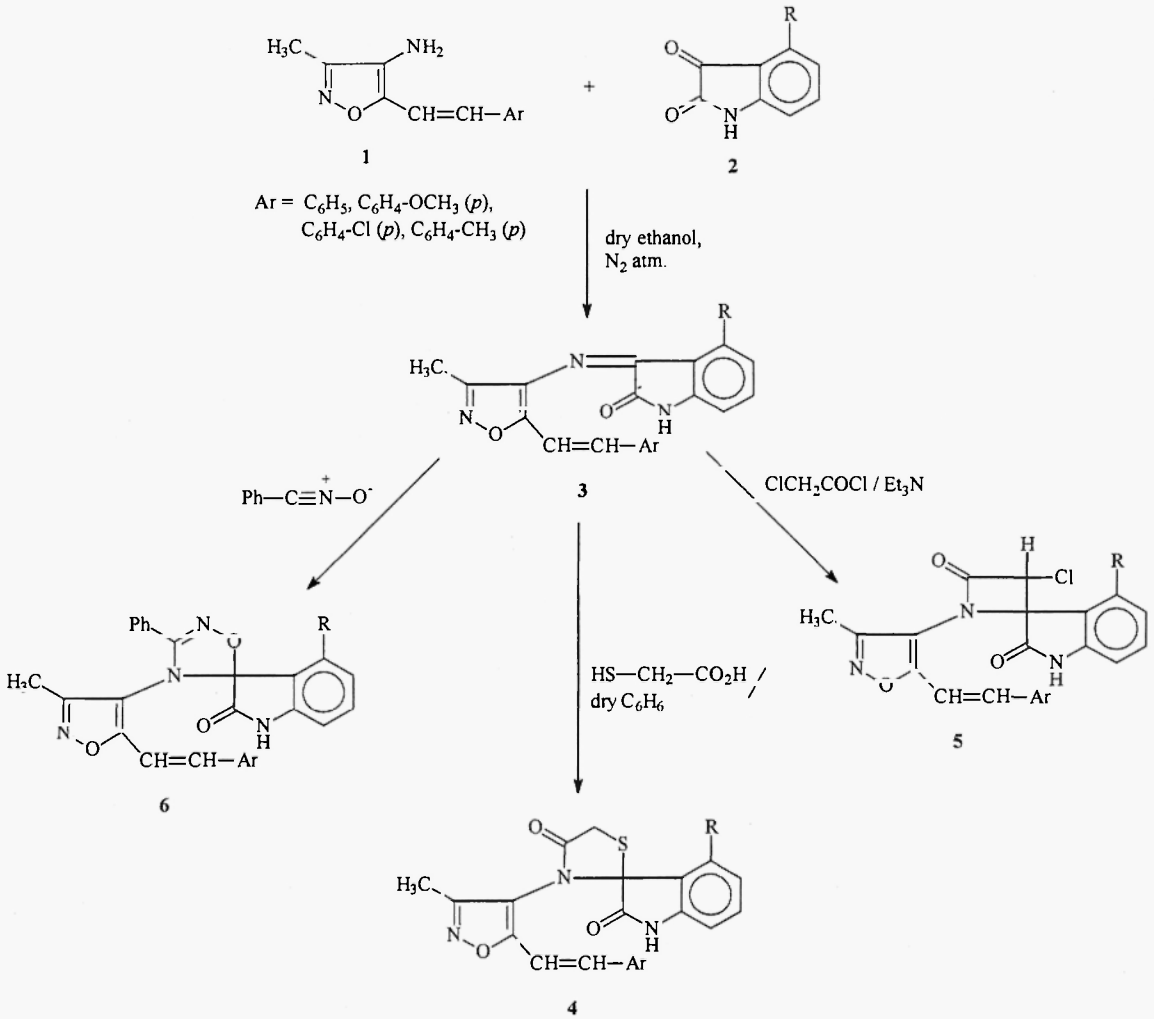
The chemistry of isoxazole derivatives continues to draw the attention of synthetic organic chemists due to their varied biological activities[1]. Several of these derivatives are potent antitumor[2], CNS-active[3], analgesic[4], antimicrobial[5] and chemotherapeutic agents[6]. Various indole derivatives show a wide range of biological properties[7-10]. If the indole ring is joined to other heterocyclic systems through a spiro-carbon atom, the resulting compounds show an increasing spectrum of biological activities. The 4-thiazolidinones[11,12], azetidinones[13-16] and 1,2,4-oxadiazolines[17,18] are of current interest due to their potent pharmaceutical importance. Encouraged by these reports and as a sequel to our work on the synthesis of isoxazole derivatives[19-22], we report, herein, the synthesis of novel and hitherto unknown new spiro-heterocyclic systems, spiro[3*H*-indole-3,2'-thiazolidine]-2,4'-(1*H*)-ones, [3*H*-indole-3,4'-azetidine]-2,2'-(1*H*)-diones) and [3*H*-indole-3,5'-3'-phenyl-1',2',4'-oxadiazoline]-2(1*H*)-ones linked to the isoxazole moiety.

The condensation of 4-amino-3-methyl-5-styrylisoxazoles **1** with different isatins **2** in dry ethanol under nitrogen atmosphere afforded 3-(3-methyl-5-styryl-4-isoxazolylimino)-2-indolinones **3**. The cyclocondensation of **3** with mercapto acetic acid has been carried out in refluxing dry benzene for 6-7 hr using a Dean-stark apparatus for the removal of water formed in the reaction. The resulting product has been identified as 3'-(3-methyl-5-styryl-4-isoxazolyl)-spiro-[3*H*-indole-3,2'-thiazolidine]-2,4-(1*H*)-diones **4** on the basis of spectral and analytical data. The IR spectra of **4** exhibited strong absorption bands around 1710, 1690 and 3350 cm^{-1} due to thiazolidinone C=O, indole C=O and indole NH functional groups respectively. The ^{1}H NMR spectra of **4** in $CDCl_3$ showed the presence of methylene protons by exhibiting a singlet at δ 4.3. The mass spectrum of **4** displayed the molecular ion peak at m/z 403 supporting the thiazolidinone formation.

The cyclocondensation of **3** with chloroacetyl chloride in dry benzene was carried out in presence of triethyl amine for 3-4 hr. The separated triethylamine hydrochloride was filtered off, the solvent was evaporated under vaccum. The residue was purified by column chromatography. The product 1'-(3-methyl-5-styryl-4-isoxazolyl)-spiro-[3*H*-indole-3,4'-azetidine)2,2'-(1*H*)-diones **5** was characterized on the basis of spectral data. The IR spectrum of **5** showed three strong absorption bands at 3275, 1675 and 1660 cm^{-1} due to NH, β-lactam carbonyl and indole carbonyl groups respectively. The ^{1}H NMR spectrum of **5** showed a one proton singlet at δ 4.2 due the azetadine ring proton and its mass spectrum showed the molecular ion at m/z 405 confirming azetidinone formation.

The interaction of benzonitrile oxide, generated *in situ* with Schiff bases **3** was carried out by stirring the reactants in chloroform at 0°C for 3 hr. The product of the cycloaddition reaction was identified 4'-(3-methyl-5-styryl-4-isoxazolyl)-spiro[3*H*-indole-3,5'-3'-phenyl-1',2',4'-oxadiazoline)-2(1*H*)-ones **6** on the basis of mass spectra. (Scheme-1) The other possible isomeric 1,2,5-oxadiazoline was not

obtained as evidenced from mass spectrum. The mass spectrum of the product **6** shows base peak at m/z 147 due to isatin (indole 2,3-dione) which could result only from the 1,2,4-oxadiazoline and not from 1,2,5-oxadiazoline, if benzonitrile oxide addition to C=N takes place in the alternate way.



1 2 3 4 5 6

Scheme-1

Experimental

Melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. IR spectra (KBr pellet) were obtained on a Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Gemini instrument at 300 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded using JEOL JMC D-300 spectrometer at 70 eV. The silica gel (0.040 x 0.063 mm) used for column chromatography was purchased from Merck. C, H and N analyses were carried out on a Carlo Erba 106 and Perkin-Elmer model 240 analysers. Physical and analytical data is included in Table-1.

Table 1 : Analytical data of compounds **3, 4, 5** and **6**

Compd.	Ar	R	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N	S
3a	C_6H_5	H	193-195	90	$C_{20}H_{15}N_3O_2$	72.85	4.56	12.70	--
						(72.94	4.55	12.76	--)
3b	C_6H_4-OCH_3(*p*)	H	180-184	85-87	$C_{21}H_{17}N_3O_3$	70.18	4.70	11.66	--
						(70.19	4.73	11.69	--)
3c	C_6H_4-Cl(*p*)	H	198-201	95	$C_{20}H_{14}N_3O_2Cl$	66.08	3.75	11.55	--
						(66.11	3.85	11.57	--)
3d	C_6H_4-Cl (*o*)	H	205-207	98	$C_{20}H_{14}N_3O_2Cl$	66.08	3.87	11.58	--
						(66.11	3.85	11.57	--)
3e	C_6H_5	5-CH_3	155-158	79	$C_{21}H_{17}N_3O_2$	72.25	4.83	12.08	--
						(72.20	4.87	12.03	--)
3f	C_6H_5	5-OCH_3	151-153	77	$C_{21}H_{17}N_3O_3$	70.20	4.76	11.70	--
						(70.19	4.73	11.69	--)
3g	C_6H_5	5-Cl	174-178	97	$C_{20}H_{14}N_3O_2Cl$	66.12	3.82	11.60	--
						(66.11	3.85	11.57	--)
3h	C_6H_5	5-Br	209-211	96	$C_{20}H_{14}N_2O_3Br$	58.10	3.34	10.17	--
						58.11	3.38	10.16	--)
4a	C_6H_5	H	165-168	95	$C_{22}H_{17}N_3O_3S$	65.55	4.25	10.48	7.96
						(65.50	4.21	10.42	7.94)
4b	C_6H_4-OCH_3(*p*)	H	138-141	87	$C_{23}H_{19}N_3O_4S$	63.79	4.33	9.64	7.37
						(63.74	4.38	9.69	7.39)
4c	C_6H_4-Cl(*p*)	H	170-173	97	$C_{22}H_{16}N_3O_3SCl$	60.43	3.60	9.66	7.38
						(60.41	3.66	9.61	7.32)
4d	C_6H_4-Cl (*o*)	H	181-183	98	$C_{22}H_{16}N_3O_3SCl$	60.45	3.69	9.65	7.35
						(60.41	3.66	9.61	7.32)
4e	C_6H_5	5-CH_3	155-158	78	$C_{23}H_{19}N_3O_3S$	66.20	4.59	10.10	7.62
						(66.18	4.55	10.07	7.67)
4f	C_6H_5	5-OCH_3	143-145	63-68	$C_{23}H_{19}N_3O_4S$	63.71	4.33	9.62	7.40
						(63.74	4.38	9.69	7.39)
4g	C_6H_5	5-Cl	168-172	90	$C_{22}H_{16}N_3O_3SCl$	60.46	3.61	9.66	7.37
						(60.41	3.66	9.61	7.32)
4h	C_6H_5	5-Br	203-208	98	$C_{22}H_{16}N_3O_3SBr$	54.84	3.37	8.79	6.60
						(54.88	3.32	8.73	6.65)
5a	C_6H_5	H	176-179	97	$C_{22}H_{16}N_3O_3Cl$	65.19	3.91	10.39	--
						(65.18	3.95	10.37	--)
5b	$C_6H_4OCH_3$(*p*)	H	168-170	88	$C_{23}H_{18}N_3O_4Cl$	63.49	4.18	9.60	--
						(63.44	4.13	9.65	--)
5c	C_6H_4-Cl(*p*)	H	185-188	85	$C_{22}H_{15}N_3O_3Cl_2$	60.17	3.46	9.51	--
						60.13	3.41	9.56	--)

Table 1 (Continued) : Analytical data of compounds **3, 4, 5** and **6**

5d	C_6H_4-Cl(*o*)	H	196-198	95	$C_{22}H_{15}O_3N_3Cl_2$	60.18	3.45	9.50	--
						60.10	3.41	9.56	--)
5e	C_6H_5	5-CH_3	174-176	80%	$C_{23}H_{18}N_3O_3Cl$	65.81	4.24	10.07	--
						65.87	4.29	10.02	--)
5f	C_6H_5	5-OCH_3	166-169	89	$C_{23}H_{18}N_3O_4Cl$	63.49	4.18	9.60	--
						(63.44	4.13	9.65	--)
5g	C_6H_5	5-Cl	205-206	98	$C_{22}H_{15}N_3O_3Cl_2$	60.16	3.48	9.59	--
						(60.13	3.41	9.56	--)
5h	C_6H_5	5-Br	209-214	98	$C_{22}H_{15}N_3O_3ClBr$	54.69	3.15	8.62	--
						(54.65	3.10	8.69	--)
6a	C_6H_5	H	145-148	97	$C_{27}H_{20}N_4O_3$	72.36	4.40	12.58	--
						(72.32	4.46	12.50	--)
6b	C_6H_4-OCH_3(*p*)	H	152-154	86	$C_{28}H_{22}N_4O_4$	70.30	4.66	11.79	--
						(70.29	4.60	11.71	--)
6c	C_6H_4-Cl(*p*)	H	170-173	93	$C_{27}H_{19}N_4O_3Cl$	67.24	3.96	11.64	--
						(67.21	3.94	11.61	--)
6d	C_6H_4-Cl(*o*)	H	186-189	89	$C_{27}H_{19}N_4O_3Cl$	67.23	3.95	11.63	--
						(67.21	3.94	11.61	--)
6e	C_6H_5	5-CH_3	165-167	90	$C_{28}H_{22}N_4O_3$	72.77	4.70	12.06	--
						(72.72	4.76	12.12	--)
6f	C_6H_5	5-OCH_3	158-160	77	$C_{28}H_{22}N_4O_4$	70.21	4.68	11.78	--
						(70.29	4.60	11.71	--)
6g	C_6H_5	5-Cl	193-199	98	$C_{27}H_{19}N_4O_3Cl$	67.26	3.90	11.66	--
						(67.21	3.94	11.61	--)
6h	C_6H_5	5-Br	203-205	95	$C_{27}H_{19}N_4O_3Br$	61.60	3.65	10.69	--
						(61.59	3.61	10.64	--)

General procedure for the preparation of 3-(3-methyl-5-styryl-4-isoxazolylmino)-2-indolinones 3

4-Amino-3-methyl-5-styrylisoxazole **1** (0.01 mole) and isatin (0.01 mole) were refluxed in dry ethanol (10 ml) for 48 hr. under nitrogen atmosphere. The solvent distilled off under vacuum and the crude product was crystallized from ethanol.

General procedure for the preparation of 3'-(3-methyl-5-styryl-4-isoxazolyl)-spiro-[3*H*-indole-3,2'-thiazolidine]-2,4'-(1*H*)-diones 4.

A mixture of **3** (0.01 mole) and mercapto acetic acid (0.01 mole) was refluxed in dry benzene using Dean-Stark apparatus for 6 hr. The residue obtained after the removal of solvent under vacuum was passed through column. Elution with petroleum ether-ethyl acetate gave the product.

General procedure for the preparation of 1'-(3-methyl-5-styryl-4-isoxazolyl)-spiro-[3H-indole-3,4'-azetidin]-2,2'-(1H)-diones 5.

To a well stirred solution of **3** (0.01 mole) and triethyl amine (0.02 mole) in dry benzene (10 ml) was added chloroacetyl chloride (0.02 mole) dropwise at room temperature. The reaction mixture was refluxed for 4 hr. and separated triethylamine hydrochloride was removed by filtration. The solvent

was distilled under vacuum, and the crude product was purified by column chromatography by elution with dichloromethane-ethyl acetate.

General procedure for the preparation of 4'-(3-methyl-5-styryl-4-isoxazolyl)-spiro-[3*H*-indole-3,5'-3'-phenyl-1',2',4'-oxadiazoline]-2(1*H*)-ones 6.

To a solution of **3** (0.01 mole) in dry chloroform (25 ml) cooled in ice-salt bath, a solution of benzhydroxamoyl chloride (0.01 mole) in chloroform was added. Triethyl amine (10 ml) in chloroform was added to the reaction mixture at 0°C during 30 min with continuous stirring. After the addition was completed, the stirring was continued for another 4 hr at 0°C. The chloroform layer was washed with water twice to free it form triethylamine hydrochloride and dried over Na_2SO_4. The solvent was distilled off and crude product was passed through silica gel column and the product was eluted with benzene-ethyl acetate.

Spectra of Representative Compounds

3a : IR (KBr) : 3465 (NH), 1730 (C=O), 1615 (C=N) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.3 (s, 3H, CH_3), 6.8 (d, 1H, CH=CH), 7.0 (d, 1H, CH=CH), 7.1-7.4 (m, 9H, Ar-H), 9.0 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 329 (M^+).

3h : IR (KBr) : 3285 (NH), 1720 (C=O), 1620 (C=N) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.4 (s, 3H, CH_3), 6.8 (d, 1H, CH=CH), 6.9 (d, 1H, CH=CH), 7.2-7.6 (m, 8H, Ar-H), 9.2 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 407 (M^+).

4a : IR (KBr) : 1705 (C=O), 1725 (C=O), 3290 (NH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.4 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 6.8 (d, 1H, CH=CH), 7.0 (d, 1H, CH=CH), 7.3-7.6 (m, 9H, Ar-H), 7.9 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 403 (M^+).

4h : IR (KBr) : 1710 (C=O), 1720 (C=O), 3285 (NH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.3 (s, 3H, CH_3), 4.2 (s, 1H, CH_2), 6.8 (d, 1H, CH=CH), 6.9 (d, 1H, CH=CH), 7.1-7.4 (m, 8H, Ar-H), 8.0 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 481 (M^+).

5a : IR (KBr) : 1675 (C=O), 1650 (C=O), 3275 (NH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.2 (s, 3H, CH_3), 4.2 (s, 1H, CH), 6.8 (d, 1H, CH=CH), 7.2 (d, 1H, CH=CH), 7.3-7.6 (m, 9H, Ar-H), 7.9 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 405 (M^+).

5h : IR (KBr) : 1680 (C=O), 1660 (C=O), 3295 (NH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.3 (s, 3H, CH_3), 4.0 (s, 1H, CH), 6.8 (d, 1H, CH=CH), 7.0 (d, 1H, CH=CH), 7.1-7.4 (m, 8H, Ar-H), 8.1 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 483 (M^+).

6a : IR (KBr) : 1690 (C=O), 1615 (C=N), 3290 (NH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.2 (s, 3H, CH_3), 6.8 (d, 1H, CH=CH), 6.9 (d, 1H, CH=CH), 7.0-7.1 (m, 14H, Ar-H), 8.5 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 448 (M^+).

6h : IR (KBr) : 1695 (C=O), 1620 (C=N), 3300 (NH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) : δ 2.3 (s, 3H, CH_3), 6.9 (d, 1H, CH=CH), 7.1 (d, 1H, CH=CH), 7.2-7.5 (m, 13H, Ar-H), 8.2 (bs, 1H, NH, D_2O exchangeable) ; MS : m/z 526 (M^+).

Acknowledgements

The authors are thankful to Prof. G. Bala Swamy, Head, Department of Chemistry, Kakatiya University for providing facilities and for his encouragement. Thanks are due to RSIC, Lucknow and IICT, Hyderabad for providing mass spectra and ^1H NMR spectra respectively.

References

1. J.B. Wakefield, J.D. Wright, "*Advances in Heterocyclic Chemistry*" (A.R. Katritzky ed.), 25 (Academic Press, New York) (1979).
2. Getal, *J. Antibiot.* **28(1)**, 91 (1975).
3. Eugster, *Prog. Chem. Org. Nat. Prod.* **27**, 261 (1969).
4. H. Kano, I. Adachi, R. Kido, K. Hirose, *J. Med. Chem.* **10(3)**, 411 (1967).
5. P.B. Reddy, S.M. Reddy, E. Rajanarendar, A.K. Murthy, *Indian Phytopathology* **37**, 370 (1984).
6. A. Sadanandam, M.V. Rajam, K. Subash, E. Rajanarendar, *Indian Bot. Report* **3(1)**, 38 (1984).
7. P. Kumar, C. Nath, K.P. Bhargava, K. Shanker, *Indian J. Chem.* **21B**, 1128 (1982).
8. Y. Kawashima, I. Amanuma, M. Sata, S. Nakashima, Y. Kaorusou, I. Noriguichi, *J. Med. Chem.* **29**, 284 (1986).
9. S.P. Hiremath, A. Ullagaddi, M.G. Purohit, *Indian J. Chem.* **27B**, 1102 (1988).
10. K.C. Joshi, A. Dandia, S. Bhagat, *Indian J. Chem.* **29B**, 766 (1990).
11. M.I. Hussain, S. Shukla, *Indian J. Chem.* **25B**, 545 (1986).
12. N. Joshi, R. Patel, H. Parekh, *Indian J. Chem.* **35B**, 867 (1996).
13. M.S. Manhas, A.K. Bose, "*Synthesis of pencillin, cephalosporin C and analogs*" (Marcel Dekker, New York), p.13 (1969).
14. R. Singh, R.D.G. Cooper, *Tetrahedron* **50**, 12049 (1994).
15. G.A. Koppel, "*Small ring heterocycles*" (Wiley Inter-Sciences, New York), (1983).
16. A.K. Bose, M.S. Manhas, J.C. Kapur, S.D. Sharma, S.G. Amine, *J. Med. Chem.* **17**, 54 (1974).
17. Bock, G. Mark, Cragoe, J. Edward, Jr. Smith, L. Robert, C. Merck and Co., Inc., Vs 4, 362, 724, (Cl. 424-246; A 61 K31/50) 07 Dec., 1982, US Appl 151, 494, 19 May, 1980 *CA* 83, 107304 C, 1983.
18. Hensen, Holger Clau; Kristionsen, Marit, Eur. Pat. Appl. EP 417, 027 (CI. 007 D487/14) 13 March, 1991, DK Appl. 89/4, 435, 08 Sep. 1989; *CA* 115, 1991, 92284.
19. E. Rajanarendar, M. Srinivas, K. Ramu, *Synth. Commun.* **33**, 3077 (2003).
20. E. Rajanarendar, K. Ramu, D. Karunakar, P. Ramesh, *J. Heterocyclic Chem.* **42**, 711 (2005).
21. E. Rajanarendar, M. Srinivas, D. Karunakar, K. Ramu, *Heterocyclic Commun.* **11**, 441 (2005).
22. E. Rajanarendar, P. Ramesh, M. Srinivas, G. Mohan, K. Ramu, *Synth. Commun.* (in press).

Received on April 6, 2006