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Synthesis and antimicrobial activity of substituted-1,3,2-oxazaphosphole 1- amines/oxide

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ABSTRACT

Synthesis of substituted-1,3,2- oxazaphospholo 1- amines/oxides was accomplished via two-step process. It involves the preparation of mono chloride intermediate **(2)** and its subsequent reaction with various substituted aromatic amines/ heterocyclic amines in dry THF in the presence of triethylamine at 50-55 ºC. These compounds were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR and MS data. All the title compounds were found to exhibit moderate anti microbial activity.

KEYWORDS

Piperidin-2-ylmethanol;
Phosphoryl chloride;
1,3,2- oxazaphospholo 1-amines/oxide.

INTRODUCTION

Organophosphorus chemistry has contributed to such diverse areas as asymmetric synthesis, biosynthesis and synthetic methodology for complex molecules. Application of chiral phosphorus reagents in asymmetric synthesis is the latest development in stereoselective organic synthesis that makes it possible to synthesize the required chiral molecule of a drug. A continued search for new and elegant methods of synthesis, improving the already known methods and forecasting new types of organophosphorus compounds and synthetic reagents remains an ever challenging problem and fascinating field to be explored these compounds continue to receive wide – spread attention due to their ubiquity in biological systems[1]. These compounds serve as possible pharmaceuticals[2], agrochemicals[3] and chemical synthetic agents[4].

Specifically organophosphorus heterocycles bearing the P-N functionality exhibited anti-tumor, pesticidal and medicinal activity[5-7]. It is noted that phosphorus compounds with N-P=O structural frame work containing different amino and phenolic groups on phosphorus as substituents are used in borane-mediated asymmetric reduction of prochiral ketones with high enantiomeric purity, where the basic cyclic moiety controls the stereo chemical course of the reaction, while the groups on the phosphorus have little significant role in directing the stereo chemical course of the reaction[8]. Synthesis of new multi-ring phosphorus heterocycles for applications in medicine and industry has attracted the attention of researchers in recent years. Phosphorus analogues of α-pyrones act as HIV protease inhibitors[9]. A number of research groups has become interested in organophosphorus heterocyclic compounds since they are finding extensive use as pesticides in agriculture, as stabilizers in polymers and as lubricant oil additives. In view of the above applications, we here in report the synthesis, spectral characterization and antimicrobial activity of novel oxazaphosphole1-amines.

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EXPERIMENTAL

Chemicals were purchased from Sigma-Aldrich, Merck and Lancaster, and were used as such without further purification. All solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods[10]. Melting points were determined using a calibrated thermometer by Guna Digital Melting point apparatus. IR spectra were recorded on a Perkin–Elmer FT-IR 240-C spectro- photometer using KBr optics. ^{1}H, ^{13}C, ^{31}P NMR spectra were recorded on a Bruker 500 MHz NMR spectrometer operating at 500 MHz for ^{1}H, 125 MHz for ^{13}C, 202 MHz for ^{31}P NMR. Spectra were recorded in DMSO-d_6 and referenced to TMS (^{1}H&^{13}C) and 85% H_3PO_4 (^{31}P). APCI mass spectra were recorded on a Jeol SX102 DA/600 Mass spectrometer. Elemental analyses were performed on a Thermo Finnigan Insturment at University of Hyderabad, Hyderabad, India.

Synthetic procedure for the title compounds (3a-j)

A solution of phosphoryl chloride (0.002 mole) in 15 mL of dry THF was added dropwise over a period of 15 minutes to a stirred solution of (piperidin-2-yl) methanol **(1)** (0.002 mole) and triethylamine (0.004 mole) in 10 mL of THF at 0-10 ºC. After stirring for 1 hour at room temperature, formation of intermediate monochloride **(2)** was ascertained by TLC analysis run in 3:7 mixture of ethyl acetate and hexane, $Et_3N.HCl$ was removed from the reaction mixture by filtration. The filtrate was evaporated in a rotary evaporator to get the intermediate **(2)**.

To a stirred solution of various aromatic/heterocyclic amines in dry THF (10 mL) and TEA (0.002 mole), the intermediate monochloride **(2)** in dry THF was added dropwise at 0 ºC. After the addition, the temperature was slowely raised to 50-55 ºC and the mixture was stirred for 2 hrs. The progress of the reaction was monitored by TLC conducted on 3:7 mixture of ethylacetate and hexane with an average R_f value 0.65. The reaction mixture was filtered to remove TEA hydrochloride and the filtrate on evaporation in a rotaevaporator yielded the crude products. These were further purified by column chromatography on silica gel (60-120 mesh) with ethyl acetate: hexane (1:9) as eluent. The title compounds were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral analyses.

Spectral data

2-Aminobenzyl-hexa hydro-[1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3a)

Yield 75%; m.p.128-29 ºC; IR(KBr) (ν_{max} cm^{-1}): 3315 (-NH), 1250 (P=O), cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 6.90-6.52 (4H, m, Ar-H), 4.49-4.25 (2H, m, -OCH_2) 3.34-3.03 (1H, m, N-CH), 2.74-2.62 (2H, m, N-CH_2), 2.51 (3H, s, NH), 1.56-1.16(6H, m, -$(CH_2)_3$); ^{13}C-NMR (DMSO-d_6) δ: 142.2 (C-1'), 129.3 (C-2'), 124.0 (C-5'),119.3 (C-4')122.2 (C-3') 115.2 (C-6'), 55.6 (C-4), 65.8 (C-3), 44.7 (C-6), 33.2 (C-7'), 30.7 (C-9), 28.0 (C-7), 23.4 (C-8); ^{31}P NMR: δ 22.0; APCI-MS m/z(%) 268 [$M^{+\cdot}$] (85), 269.3 [M+H]$^+$ (13.2); Anal. Calcd for $C_{12}H_{19}N_3O_2P$: C, 53.72, H, 7.14, N, 15.66. Found. C, 53.70, H, 7.10, N, 15.69

2-Fluoro-5-nitro-phenyl-1-oxo hexa hydro-1λ^5 [1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3b)

Yield 82%; m.p. 135-37 ºC; IR(KBr) (ν_{max} cm^{-1}): 3275 (-NH), 1263 (P=O), $^{1}HNMR$ (DMSO-d_6) δ_H: 7.90-6.89 (3H, m, Ar-H), 4.30-4.15 (2H, m, -OCH_2) 3.30-3.25 (1H, m, N-CH), 2.89-2.74 (2H, m, NH-CH_2), 2.61(1H, s, NH), 1.27-1.13(6H, m, -$(CH_2)_3$); ^{13}C-NMR (DMSO-d_6) δ: 132.3 (C-1'), 120.3 (C-3'), 162.3 (C-2'), 140.6 (C-5'), 116.4 (C-4'), 110.2 (C-6'), 55.1 (C-4), 48.9(C-3), 63.2 (C-6), 31.7 (C-9), 29.4 (C-7), 22.8 (C-8); ^{31}P NMR data: δ 22.83; APCI-MS m/z(%) 316[MH]$^{+\cdot}$ (75); Anal. Calcd for $C_{12}H_{15}FN_3O_4P$: C, 45.72, H, 4.80, N, 13.33. Found. C, 45.76, H, 4.74, N, 13.40.

3- Chloro-4- fluoro –phenyl hexa hydro [1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3c)

Yield 78%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3248 (-NH), 1260(P=O), cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 7.41 -7.29 (3H, m, Ar-H), 3.34-3.03 (1H, m, N-CH), 4.23-3.90 (2H, m, -OCH_2), 2.62-2.53 (2H, m, N-CH_2), 2.51 (1H, s, NH), 1.56-1.16 (6H, m, -$(CH_2)_3$); ^{13}C-NMR (DMSO-d_6) δ: 160.2 (C-4'), 149.5 (C-1'), 119.1 (C-5'), 121.1 (C-3'), 117.2 (C-2'), 115.4 (C-6'), 54.9 (C-4), 62.3 (C-3), 43.7 (C-6), 29.8 (C-9), 27.8 (C-7), 23.2 (C-8); ^{31}P NMR data: δ 24.20; Anal. Calcd for $C_{12}H_{15}ClFN_2O_2P$: C, 47.30, H, 4.96, N, 9.19. Found. C, 47.25, H, 5.1, N, 9.24.

2,4-Dichloro-phenyl-1-oxo hexa hydro-1λ⁵[1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3d)

Yield 76%; m.p. 126-128 ºC IR(KBr) (ν_{max} cm^{-1}): 3368(-NH), 1269(P=O) cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 7.25-6.53 (3H, m, Ar-H), 3.53-3.41 (1H, m, N-CH), 4.19-3.82 (2H, m, -OCH$_2$), 2.65-2.53 (2H, m, N-CH$_2$), 2.42 (1H, s, NH), 1.65-1.50 (6H, m, -(CH$_2$)$_3$); ^{31}P NMR data: δ 26.19;; Anal. Calcd for $C_{12}H_{15}N_2O_2P$: C, 53.46, H, 9.40, N, 13.86. Found. C, 53.38, H, 9.45, N, 13.92.

1-Oxo hexa hydro-1λ⁵[1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-thiophen-2-ylmethyl-amine (3e)

Yield 81%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3148 (-NH), 1262 (P=O) cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 7.25-6.37 (3H, m, Ar-H), 4.20-3.75 (2H, m, -OCH$_2$), 3.68-3.61 (1H, m, N-CH), 2.95-2.86 (2H, m, NH-CH$_2$), 2.71-2.65 (2H, m, N-CH$_2$), 2.55 (1H, s, NH), 1.59-1.30 (6H, m, -CH$_2$)$_3$); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 136.4 (C-2'), 122.6 (C-5'), 129.5 (C-4'), 127.5 (C-3'), 33.2 (C-6'), 58.2 (C-4), 66.1 (C-3), 42.2 (C-6), 30.5 (C-9), 29.0 (C-7), 21.6 (C-8); ^{31}P NMR data: δ 22.83; APCI-MS m/z(%) 273 [MH]$^{+\cdot}$ (80); Anal. Calcd for $C_{11}H_{17}N_2O_2PS$: C, 48.52, H, 6.29, N, 10.29. Found. C, 48.56, H, 6.32, N, 10.35.

2-1H-Imidazol-4-yl-ethyl-1-oxo hexahydro 1λ⁵ [1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3f)

Yield 79%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3367 (-NH), 1233 (P=O) cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 10.12 (1H, s, -NH), 7.12 (1H, s, Ar-H), 6.32 (1H, s, Ar-H), 4.19-3.85 (2H, m, -OCH$_2$), 3.68-3.54 (1H, m, N-CH), 2.85-2.72 (4H, m, NH-CH$_2$), 2.62-2.54 (2H, m, N-CH$_2$), 2.47(1H, s, NH), 1.89-1.16 (6H, m, -(CH$_2$)$_3$); ^{31}P NMR data: δ 26.02; Anal. Calcd for $C_{11}H_{19}N_4O_2P$: C, 48.88, H, 7.09, N, 20.73. Found. C, 48.60, H, 6.98, N, 20.77.

1-Oxo hexahydro-1λ⁵[1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl pyridine - 3-ylmethyl-amine (3g)

Yield 75%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3248 (-NH), 1260(P=O) cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 8.50 (d, 2H, *J* = 8 Hz, Pyridine-CH), 7.65-6.92 (2H, m, Ar-H), 3.92-3.85 (2H, m, -OCH$_2$), 3.34-3.03 (1H, m, N-CH), 2.96-2.90 (2H, m, NH-CH$_2$), 2.62-2.53 (2H, m, N-CH$_2$), 2.51 (1H, s, NH), 1.56-1.16 (6H, m, -(CH$_2$)$_3$); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 160.2 (C-2'), 149.5 (C-6'), 139.1 (C-4'), 121.1 (C-5'), 125.4 (C-3'), 54.9 (C-4), 65.3 (C-3), 43.7 (C-6), 39.2 (C-7'), 29.8 (C-9), 27.8 (C-7), 23.2 (C-8); ^{31}P NMR data: δ 24.20; APCI-MS m/z(%) 268[MH]$^{+\cdot}$ (85); Anal. Calcd for $C_{12}H_{18}N_3O_2P$: C, 53.93, H, 6.79, N, 15.72. Found. C, 53.96, H, 6. 73, N, 15.76

2-1H-Indol-3-yl-ethyl-1-oxo hexa hydro 1λ⁵[1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3h)

Yield 80%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3326 (-NH), 3182 (-NH), 1265 (P=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ_H: 9.90 (1H, s, Ar-NH), 7.12 - 6.76 (4H, m, Ar-H), 6.12 (1H, s, Ar-H), 3.80-3.69 (2H, m, -OCH$_2$), 3.47-3.30 (1H, m, N-CH), 3.32 (1H, s, NH), 2.96-2.82 (2H, m, N-CH$_2$), 2.89-2.72 (4H, m, NH-CH$_2$), 1.52-1.36 (6H, m, -(CH$_2$)$_3$); ^{31}P NMR data: δ 23.02; Anal. Calcd for $C_{16}H_{22}N_3O_2P$: C, 60.18, H, 6.94, N, 13.16. Found. C, 60.22, H, 7.02, N, 13.20.

1H-Benzimidazol-2-yl-ethyl-1-oxo hexa hydro 1λ⁵ [1,3,2] oxazaphospholo [3,4-a] pyridine-1-yl-amine (3i)

Yield 78%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3372 (-NH), 3182 (-NH), 1231(P=O) cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 8.12 (1H, s, Ar-NH), 7.75-6.98 (4H, m, Ar-H), 3.72-3.54 (2H, m, -OCH$_2$), 3.03-2.92(1H, m, N-CH), 2.67-2.52(2H, m, N-CH$_2$), 2.42(1H, s, -NH), 1.52-1.34(6H, m, -(CH$_2$)$_3$); ^{31}P NMR data: δ 22.12; APCI-MS m/z(%) 293 [MH]$^{+\cdot}$ (60); Anal. Calcd for $C_{13}H_{17}N_4O_2P$: C, 53.42, H, 5.86, N, 19.17. Found. C, 53.45, H, 5.90, N, 19.20.

1-Pyridin-2-ylmethoxy-hexahydro[1,3,2] oxazaphospholo [3,4-a] pyridine-1-oxide (3j)

Yield 82%; viscous liquid, IR(KBr) (ν_{max} cm^{-1}): 3248 (-NH), 1260(P=O) cm^{-1}; ^{1}H- NMR (DMSO-d_6) δ_H: 8.23 (d, 1H, *J* = 7.2 Hz, Pyridine-H), 7.53-6.85 (3H, m, Ar-H), 4.45-4.13 (4H, m, -OCH$_2$), 3.34-3.03 (1H, m, N-CH), 2.62-2.53 (2H, m, N-CH$_2$), 1.56-1.16 (6H, m, -(CH$_2$)$_3$); ^{13}C-NMR (DMSO-d_6) δ [ppm]: 158.2 (C-2'), 147.3 (C-6'), 137.2 (C-4'), 119.2 (C-5'), 121.6 (C-3'), 56.9 (C-4), 64.3 (C-3), 42.7 (C-6), 62.2 (C-7'), 29.5 (C-9), 26.4 (C-7), 23.2 (C-8); ^{31}P NMR data: δ 24.20; APCI-MS m/z(%) 269[MH]$^{+\cdot}$ (75); Anal. Calcd for $C_{12}H_{17}N_2O_3P$: C, 53.73, H, 6.39, N, 10.44. Found. C, 53.69, H, 6. 36, N, 10.52.

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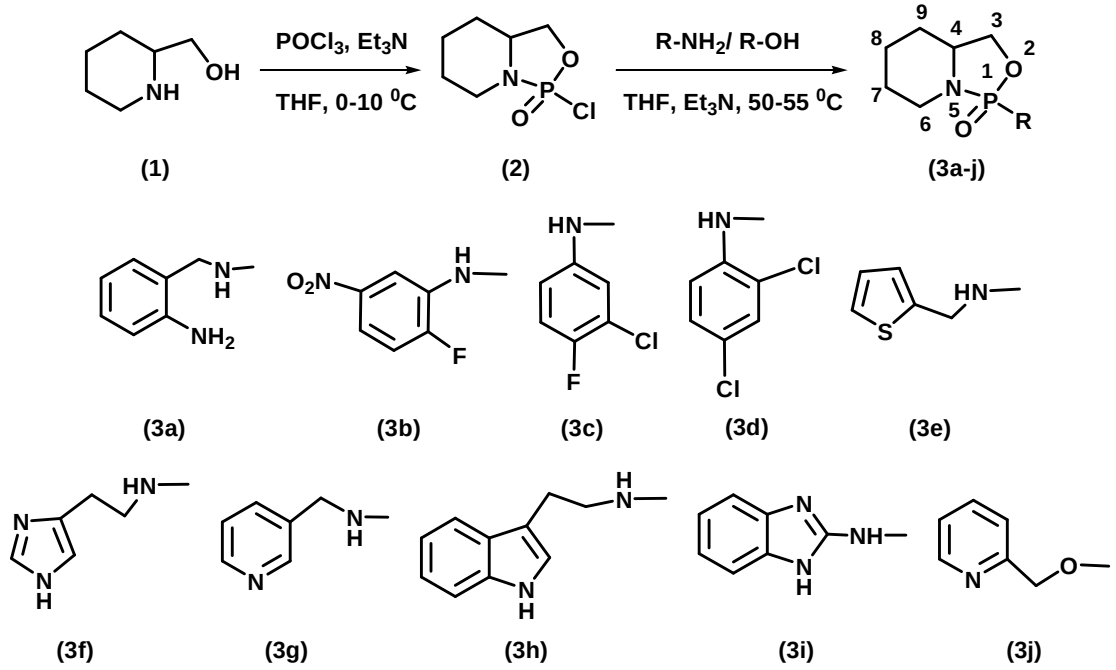
RESULTS AND DISCUSSION

The synthesis of substituted 1,3,2-oxazaphosphole 1-amines/oxides **(3a-j)** is accomplished in a two-step process (Scheme 1). The synthetic route involves the condensation of (piperidin-2-yl) methanol **(1)** with phosphoryl chloride in dry tetrahydrofuran (THF) in the presence of triethylamine (TEA) at 0-10 ºC to afford the corresponding monochloride intermediate **(2)**. In the second step the intermediate **(2)** was reacted with various substituted aromatic amines/ heterocyclic amines in dry THF in the presence of TEA to obtain the title compounds **(3a-j)** in high yields. The second step of the reaction was completed in 2-3 h at 50-55 ºC with stirring. Progress of the reaction was monitored by TLC (3:7 ethyl acetate: hexane). The cyclised products **(3a-j)** were isolated by filtration to remove $Et_3N.HCl$, followed by evaporation of the filtrate in a rotary evaporator. Further purification was carried out by washing the residue with hexane followed by column chromatography using hexane-ethyl acetate (4:1) mixture as an eluent.



Scheme 1

The compounds **(3a-j)** exhibited IR absorption bands for P=O, P-NH in the regions 1269-1214 and 3420-3250 cm^{-1}[11] respectively. The –NH proton gave a singlet at δ 3.55-2.42, the C-3 methyleneoxy hydrogens resonated as multiplets at δ 4.40-3.90. The N-CH proton gave a multiplet at δ 3.68-2.92. In the ^{13}C-NMR spectra, C-3 resonated at δ 68.3-66.8. The remaining carbon resonances are observed in the expected region. ^{31}P-NMR chemical shifts were observed in the region 22.19-15.94 ppm[12]. The LC-MS data of **(3a-j)** showed their protonated molecular ions.

Antimicrobial activity

All the compounds **(3a-j)** were screened for their antibacterial activity against *Staphylococcus aureus, Klebsiella pneumoniae* and antifungal activity against *Pellicularia solamnicolor, Macrophomina phaseolina*. The *in vitro* anti bacterial activity of the compounds was tested by disc diffusion method[13] in nutrient agar medium at two different concentrations (100, 300 μg/mL) in DMSO. The solutions were added to each filter disc, and the plates were incubated at 36 °C and examined for zone of bacterial inhibition around each disc after 24 h. Results were compared with the activity of the standard antibiotic Penicillin. The *in vitro* antifungal activity of the compounds were tested by disc diffusion method[14] at two different concentrations (100, 300 μg/mL) in DMSO. Fungal cultures were grown on potato dextrose agar at 25 °C and spore suspension was adjusted to 10^5 spores/mL. Results were compared with the activity of the standard anti fungal agent Griseofulvin.

The obtained results were presented in TABLE 1.

In general all the synthesized compounds showed moderate anti bacterial activity *in vitro* against the tested organisms. Most of the compounds showed good antibacterial activity due to the presence of different substituted aromatic and heterocyclic rings.

TABLE 1 : Antibacterial activity of compounds (3a-j) against gram positive and gram negative bacteria.

Compounds	Zone of Inhibition (mm)			
	S. aureus		*K. pneumoniae*	
	100 µg/mL	300 µg/mL	100 µg/mL	300 µg/mL
3a	18	37	21	42
3b	15	37	20	40
3c	19	40	22	42
3d	20	41	21	41
3e	15	35	19	35
3f	16	33	18	34
3g	17	32	18	37
3h	19	37	16	32
3i	18	36	17	35
3j	19	38	16	34
Penicillin	22	41	24	46

The obtained results are presented in TABLE 2. The results suggest that the differently substituted compounds of the aryl and heterocyclic rings **(3a-j)** showed moderate antifungal activity against both the fungi.

TABLE 2 : Antifungal activity of compounds (3a-j).

Compounds	Zone of Inhibition (mm)			
	P. solamnicolor		*M. phaseolina*	
	100 µg/mL	300 µg/mL	100 µg/mL	300 µg/mL
3a	18	40	20	42
3b	17	39	19	41
3c	19	41	22	42
3d	20	43	21	40
3e	18	37	18	36
3f	15	36	17	34
3g	18	37	16	39
3h	17	35	18	36
3i	19	40	18	38
3j	18	39	19	37
Griseofulvin	22	44	24	46

CONCLUSION

Synthesis of a series of novel 1-substituted-1,3,2-diazaphosphole 1-oxides is accomplished by adopting a simple and straight forward synthetic protocol. The structures of **3a-l** were established by elemental analysis, IR, NMR (^{1}H, ^{13}C and ^{31}P) and mass spectral data.

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REFERENCES

[1] F.H.Westheimer; Science, **235**, 1173 **(1987)**.
[2] P.Kafarski, B.Lejczak; Curr.Med.Chem., 301 **(2001)**.
[3] J.E.Franz, M.K.Mao, J.A.Sikorski; Glyphosate: A Unique Global Herbicide, American Chemical Society, Washington, DC, USA, **(1997)**.
[4] B.E.Maryanoff, A.B.Reitz; Chem.Rev., **89**, 863 **(1989)**.
[5] M.Venugopal, B.Sankar Reddy, C.Devendranath Reddy, K.D.Berlin; J.Heterocycl.Chem., **38**, 275 **(2001)**.
[6] A.R.Katritzky, C.W.Rees, E.F.V.Scriven; Comprehensive Heterocyclic Chemistry II, Pergmon Press: Oxford, U.K., **(1996)**.
[7] P.V.G.Reddy, Y.H.Babu, C.S.Reddy, D.Srinivasulu; Heteroatom Chem., **13**, 340 **(2002)**.
[8] D.Basavaiah, G.J.Reddy, V.Chandrashekar; Tetrahedron: Asymmetry, **12**, 685 **(2001)**.
[9] A.M.Polozov, S.E.Cremer; J.Organomet.Chem., **646**, 153 **(2002)**.
[10] W.L.F.Armarego, D.D.Perrin; Purification of Laboratory Chemicals, Fourth Edition, Butterworth, Heinemann, Oxford, OX2, 8DP **(1997)**.
[11] R.M.Silverstein, F.X.Webster; Spectrometric Identification of Organic Compounds, John Wiley & Sons, New York, **(1998)**.
[12] R.Wang, S.Harada, H.Mitsuya, J.Zemlicka; J.Med. Chem., **22**, 4799 **(2003)**.
[13] R.Cruickshank; Medical Microbiology, A Guide to Diagnosis and Control of Infection, 2nd Edition, E.S. Livingston Ltd., Edinburgh and London, **(1968)**.
[14] H.J.Benson; Microbiological Applications, 5th Edition, W.C.Brown, Dubuque, Iowa, **(1990)**.