α-*N*-Methyl/phenyl furan derivatives as dipolarophiles for synthesis of spiro isoxazolidine derivatives with α-chloro and simple nitrones

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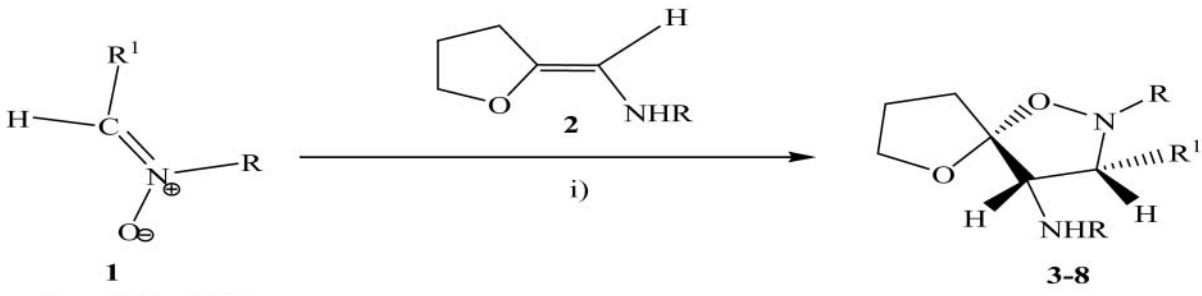
1,3-Dipolar cycloaddition reactions of α-chloro and simple nitrones have been studied with novel α-*N*-methyl/phenyl furan derivatives as new dipolarophiles. The reactions are found to be highly regioselective to afford single 5-spiro isoxazolidines with high yield in a short reaction time.

Keywords: α-*N*-methyl/phenyl furan derivatives, spiro cycloadducts, regioselectivity

In addition to the reported dipolarophiles for 1,3-dipolar cycloaddition reactions of nitrones,[1] we now describe some further novel and efficient dipolarophiles (α-*N*-methyl/phenyl furan derivatives) for the cycloaddition reactions to afford solely 5-spiro isoxazolidines with high yield in a very short reaction time (4–6 h) with different nitrones at RT (Scheme 1). A detailed literature survey reveals that these type of cycloaddition reactions are generally diastereomeric in nature with the predominance of one of the isomers.[2] The synthetic potential of α-chloro nitrones (**1**) has been proved not only in cycloaddition reactions but also in the synthesis of novel dipolarophiles (**2**) when treated with alkyl halides.[3] α-*N*-methyl/phenyl furan derivatives (**2**) were isolated as side-products and in single *E* isomeric forms (almost 20%) in the reported oxidation reaction of alkyl halides to aldehydes and ketones using α-chloro nitrones[4–8] (Scheme 2). The novel 5-spiro isoxazolidines (**3–8**) were predominantly obtained regioselectively in high yields (78–88%) as single isomers in the reactions of α-chloro, α-amino and simple nitrones. This could be due to the fact that the nitrone (LUMO)–dipolarophile (HOMO) interactions are strong enough to dominate the reaction[9–11] and lead to the formation solely of 5-spiro cycloadducts (**3–8**) via an *exo* approach of the nitrone **1** (all the reported nitrones have a *Z* configuration) to the furan derivatives **2** (transition state **1**). At the outset of this work it was unclear whether the side-products obtained during aldehyde and ketone synthesis could be employed as efficient dipolarophiles. For the present study, we have used five different nitrones: *N*-methyl-α-chloro nitrone,[6] *N*-phenyl-α-chloro nitrone,[8] *N*-methyl-α-amino nitrone,[12] *N*-phenyl-α-amino nitrone[13–15] and *N*-methyl/phenyl nitrones[16] respectively in order to generalise regioselectivity in cycloaddition reactions using novel dipolarophiles (**2**). The stereochemistry of the isoxazolidine derivatives (**3–8**) were rationalised by considering the multiplicity of the proton signals at 3-H, 4-H, CHCl (in the case of α-chloro nitrones only) asymmetric centres along with their coupling constant values.[17,18] In the ^{1}H NMR spectrum of cycloadducts **3–4**, 3-H resonates around δ_H 2.50–3.50 ppm while 4-H around δ_H 3.00–5.85 ppm and the coupling constant is $J_{3,4}$ ~ 9.16 Hz implying a *cis* relationship between H-3 and H-4. The CHCl proton also resonates upfield around δ_H 2.20–2.60 ppm. The 3-H and CHCl protons are also *syn* as evidenced from their coupling constant values ($J_{3,CHCl}$ ~ 9.40 Hz).[17,18] Almost similar coupling constant values are obtained for H-3 and H-4 protons in the case of other reported cycloadducts (**5–8**). Cycloaddition of *Z* nitrone via *exo*-transition state geometry results in *syn* spiro isoxazolidine derivatives. The ^{1}H NMR spectra of **3–8** also show significant long range coupling between H-4 with H-3' and vice-versa in most of the spiro cycloadducts. In the mass spectra, in addition to molecular ion peaks, prominent base peak values are obtained in all the cycloadducts and significant M+2 peaks of characteristic relative heights are also obtained in **3–4** which is due to the isotopic abundance of Cl^{37} atoms. Studies of HRMS spectra show almost exact masses for the majority of the compounds. The experimental procedure is very simple. α-*N*-methyl/phenyl furan derivatives (**2**) are added to nitrone **1** in diethyl ether at RT. Smooth reaction ends with the production of the novel spiro cycloadducts with extremely good yield in a very short reaction time. In general, the reactions are very clean and high yielding compared to other cycloaddition reactions of α-chloro and α-amino nitrones.[1,3–8,13–15] The products are characterised from their spectroscopic (IR, ^{1}H NMR, HRMS, ^{13}C NMR) data. No catalyst or co-organic solvent is required. All the novel isoxazolidine derivatives (**3-8**) were also screened for antibacterial activity and found to be very active.

A preferential conformation for the spiro cycloadducts (**3–8**) is shown in Fig. 1.

A new mechanistic pathway for the synthesis of novel dipolarophiles (α-*N*-methyl/phenyl furan derivatives) may be represented in the following mechanism[3] (Scheme 2).



Scheme 1

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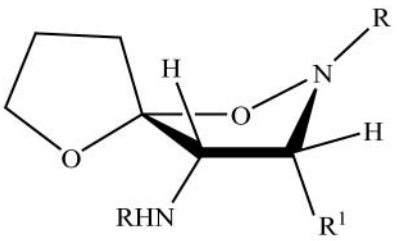
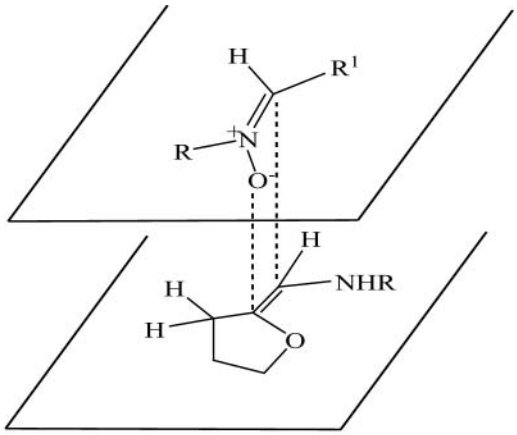


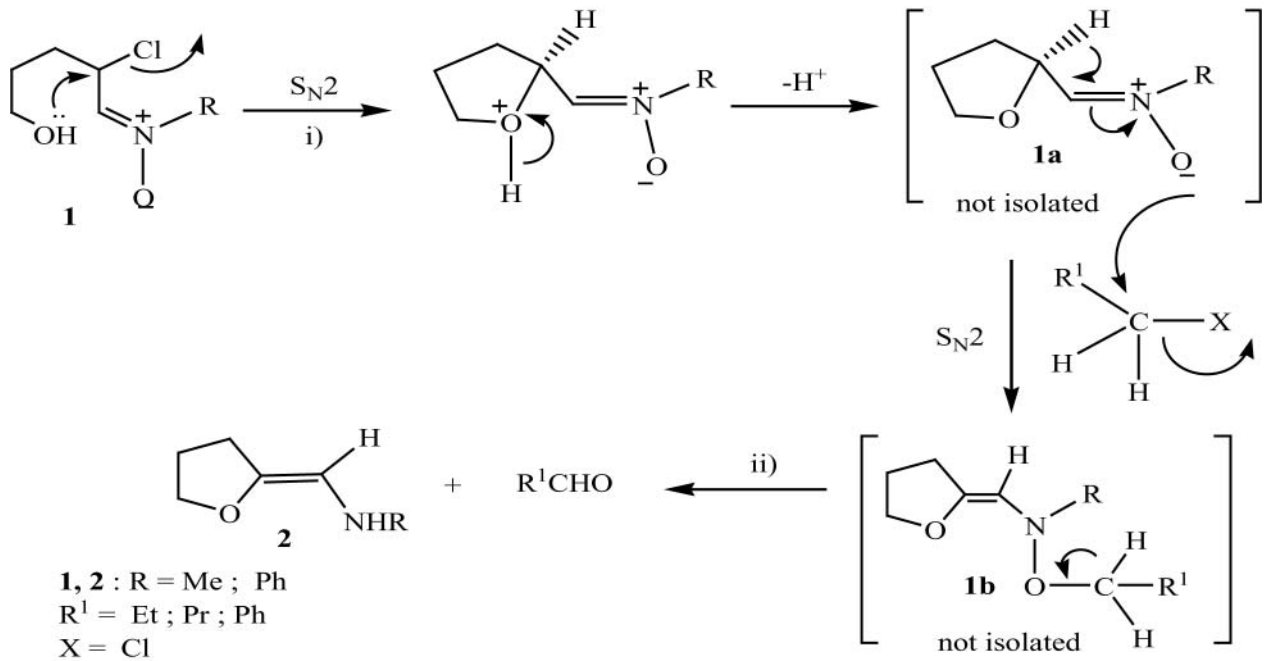
R^1 = Ph, NH_2, $CHCl(CH_2)_3OH$

General conformation for the spirocycloadducts (**3-8**)



TS 1 for forming spiro cycloadducts (**3-8**)

Fig. 1



Reagents and conditions : i) Dry ether, pyridine, r.t , N_2 atmosphere

ii) Dry ether, Na_2CO_3, r.t , N_2 atmosphere

Scheme 2

Finally, we have reported the synthesis of novel spiro cycloadducts using novel dipolarophiles with different nitrones in 1,3-dipolar cycloaddition reaction. The formation of the desired compounds was obtained in good yields within a short reaction time. The notable advantages offered by this method are one-pot synthesis, simple operation, easy workup, mild and faster reaction conditions with high yield of products.

Experimental

^{1}H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. The HRMS spectra were recorded on a Q–Tof micro instrument (YA–105). TLC's were run on Fluka silica gel precoated TLC plates while column chromatography was performed with silica gel (E.Merck India) 60–200 mesh. All the alkyl halides, reagents and solvents were purified after receiving from commercial suppliers. *N*-methylhydroxylamine was purchased from Aldrich Chemical Company and was used as received. *N*-Phenylhydroxylamine was prepared following standard methods available in the literature and has been used already for the reported synthesis of aldehydes and in cycloaddition reactions involving α-amino, α-chloro nitrones in aqueous phase and in organic solvents.[3–8,12–15]

General procedure for synthesis of aldehyde and furan derivatives **2**
To a stirred solution of nitrone **1** (R=Me; 500mg, 3.0198 mmol) in dry ether (25 ml) was added pyridine (1 equivalent) and stirred at RT with a magnetic stirrer under N_2 atmosphere for 1 h while the formation of transient nitrone **1a** (not isolated) was monitored by TLC (R_f = 0.38). Benzyl chloride (292.mg, 1 equiv) was added at this stage and the reaction mixture was stirred for another 3 h until the intermediate

compound **1b** (not isolated) was developed (monitored by TLC; R_f = 0.40). Solid Na_2CO_3 (2g.) was added at this stage and the reaction mixture was stirred for a further 1 h while the progress of the reaction was again monitored by TLC (R_f = 0.43, 0.50). During this process the N–O bond was cleaved in the basic medium.[19] Basic workup, removal of pyridine hydrochloride and silica gel column chromatographic purification using ethyl acetate-hexane provided the desired benzaldehyde as a colourless liquid (702 mg, 82%) and α-*N*-phenyl furan derivative (**2**) as a pale yellow gummy liquid (88mg, 17%). This procedure was followed for the synthesis of α-*N*-methyl furan derivative with other alkyl halides.

General procedure for cycloaddition (for regioselective spiro cycloadducts)

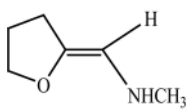
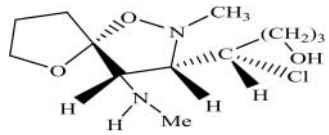
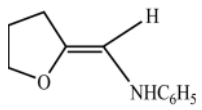
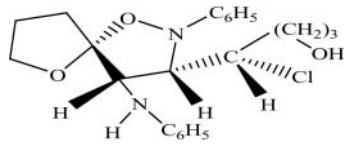
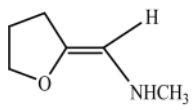
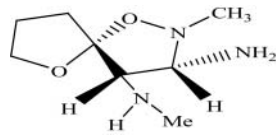
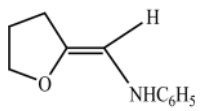
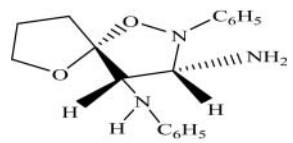
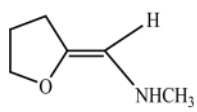
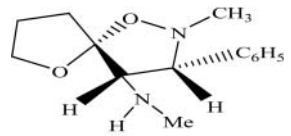
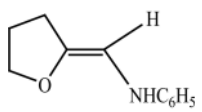
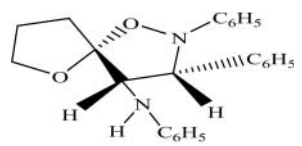
To a well stirred solution of nitrone **1** (**R=Me**; 1 mmole) in diethyl ether (20 mL) taken in a 50 mL conical flask, was added the α-*N*-methyl furan derivative [(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-methyl methanamine)] (1 equiv) which was stirred at RT with a magnetic stirrer under N_2 atmosphere for 4 h. The progress of the reaction was monitored by TLC (R_f = 0.53). After completion of the reaction and work-up, the crude spiro-cycloadduct was concentrated in a rotary evaporator and finally purified by column chromatography using ethyl acetate - hexane to afford pure spiro-cycloadduct **3** (entry 1, Table 1, Scheme 1). This procedure was followed for the reaction of nitrone **1** (R= Me,Ph) with the α-*N*-methyl/phenyl furan derivatives **2** [(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-methyl methanamine)/(*E*)-1-(dihydrofuran-2-(3H)-ylidene)-*N*-phenyl methanamine)] listed in Table 1.

(R=Me; α*-N-methyl furan derivative) [(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-methyl methanamine)]* (**2**): IR (KBr): 3125–3054 (br), 2838 (m), 1652 (s), 1455 (m), 1210 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.81 (br, 1H, N-H), 4.56 (s, 1H, C=CH), 3.30 (N-Me), 2.50–2.16 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 103.00, 101.76 (double bonded carbons), 26.22, 25.30, 23.65 (3 CH_2 carbons); FAB–MS: *m/z* 113 (M^+), 98, 97; HRMS-EI: Calcd for $C_6H_{11}ON$ (M), 113.1000. Found: M^+, 112.9876.

(R=Ph; α*-N-phenyl furan derivative) [(E)-1-(dihydrofuran-2-(3H)-ylidene)-N-phenyl methanamine)]* (**2**): IR (KBr): 3150-3060 (br), 2860 (m), 1640 (s), 1430 (m), 1140 (m), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.83 (m, 5H, C_6H_5), 6.29 (br, 1H, N-H), 2.17 (s, 1H, C=CH), 1.79–1.18 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 137.20, 135.65, 134.00, 132.15 (aromatic carbons), 106.24, 104.18 (double bonded carbons), 28.46, 27.10, 24.84 (3 CH_2 carbons). FAB–MS (*m/z*): 175 (M^+), 98, 97, 77. HRMS-EI: Calcd for $C_{11}H_{13}ON$ (M), 175.0993. Found: M^+, 175.0981.

(S)-4-Chloro-4-((3S,4S,5R)-2methyl-4-(methylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol (**3**): Pale yellow gummy liquid. Yield 88%, R_f = 0.53; IR (KBr): 3460–3326 (br), 2948 (m), 2420 (m), 1485 (s), 1325 (m), 810 (m), 774 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.83 (br, 1H, CH_2OH, exchanged in D_2O), 4.60 (s, 1H, $NHCH_3$), 3.37

Table 1 Cycloaddition reaction of nitrone **1** with novel dipolarophiles (**2**)

Entry	Nitrone (**1**)	Novel dipolarophiles[a] (**2**)	Spiro cycloadducts[b] (**3–8**)	Time /h	Nature of products	Yield /%[c]
1	R = Me R^1 = $CHCl(CH_2)_3OH$		 **3**	4	Pale yellow gummy liquid	88
2	R = Ph R^1 = $CHCl(CH_2)_3OH$		 **4**	5	Dark red viscous liquid	86
3	R = Me R^1 = NH_2		 **5**	5	Grey viscous liquid	84
4	R = Ph R^1 = NH_2		 **6**	6	Dark grey viscous liquid	81
5	R = Me R^1 = Ph		 **7**	5	Colourless gummy liquid	78
6	R = R^1 = Ph		 **8**	6	Colourless gummy liquid	78

[a] Reaction conditions: nitrone (1 mmole), furan derivative (1 equiv),dry ether, N_2atmosphere, RT.
[b] All the spiro cycloadducts were characterised by IR, ^1H NMR, MS, ^{13}C NMR spectral data.
[c] Isolated yield after purification.

(s, 6H, 2 x N-CH_3), 3.12 (dd, 1H, *J* = 9.20, 8.32 Hz, C_3H), 2.70 (dt, 1H, *J* = 8.10, 7.88 Hz, C_4H), 2.35 (dt~m, 1H, CHCl), 1.88–1.42 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 93.00 (CHCl), 87.55 (C_5), 76.20 (C_3), 55.20 (C_4), 41.97 (N-CH_3), 40.24 (NH-CH_3), 33.37, 31.50, 28.68, 26.00, 25.12, 23.40 (6 CH_2 carbons); MS (*m/z*): 280 (M^++2), 278 (M^+), 263, 248, 156 (B.P), 141, 107; HRMS-EI: Calcd for $C_{12}H_{23}O_3N_2Cl$ (M), 278.6710. Found: M^+, 278.6698.

(S)-4-Chloro-4-((3S,4S,5R)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol (**4**): Dark red viscous liquid. Yield 86%, R_f = 0.48; IR (KBr): 3485–3290 (br), 2962 (m), 2425 (m), 1620 (s), 1490 (s), 1260 (m), 1040 (m), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.98 - 6.92 (m, 10H, 2 x C_6H_5), 5.84 (dd, 1H, *J* = 8.55, 8.20 Hz, C_3H), 5.00 (br, 1H, CH_2OH, exchanged in D_2O), 3.60 (dt, 1H, *J* = 9.34, 7.88 Hz, C_4H), 3.40 (s, 1H, N–H proton of NHPh), 2.68 (dt~m, 1H, CHCl), 1.90 (dt, 1H, *J* = 6.82, 6.64 Hz, C_3H), 1.50–1.12 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 138.00, 136.50, 134.30, 133.80, 131.75, 130.42, 129.46, 128.64 (aromatic carbons), 95.10 (CHCl), 86.40 (C_5), 73.75 (C_3), 53.30 (C_4), 30.20, 28.55, 27.34, 26.22, 25.73, 24.37 (6 CH_2 carbons); MS (*m/z*): 404 (M^++2), 402 (M^+), 325, 310, 309, 218 (B.P), 107, 91, 77. HRMS-EI: Calcd for $C_{22}H_{27}O_3N_2Cl$ (M), 402.7130. Found: M^+, 402.7122.

(S)-3-Amino-(3S,4S,5S)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiroisoxazole (**5**): Grey viscous liquid. Yield 84%, R_f = 0.52; IR (KBr): 3430–3380 (br), 3033 (m), 2955 (m), 1773 (s), 1662 (s), 1480 (s), 1282 (m), 1178 (s), 806 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.90 (br,s, 2H, NH_2, exchanged in D_2O), 4.60 (br, 1H, $NHCH_3$), 3.36 (s, 6H, 2 x N-CH_3), 3.00 (d, 1H, *J* = 7.54 Hz, C_3H), 2.70 (dt, 2H, *J* = 6.24, 6.28 Hz, C_3'2H), 2.38 (dt, 1H, *J* = 7.12, 6.70 Hz, C_4H), 1.70–1.48 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 88.50 (C_5/$C_{2'}$), 77.12 (C_3), 56.26 (C_4), 40.94 (N-CH_3), 38.13 (NH-CH_3), 32.07, 31.22, 29.34 (3',4',5' CH_2 carbons); MS (*m/z*): 187 (M^+), 172, 157, 156 (B.P), 141. HRMS-EI: Calcd for $C_8H_{17}O_2N_3$ (M), 187.1633. Found: M^+, 187.1613.

(S)-3-Amino-(3S,4S,5S)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiroisoxazole (**6**): Dark grey viscous liquid. Yield 81%, R_f = 0.48; IR (KBr): 3436–3390 (br), 3030 (m), 2952 (m), 1780 (s), 1674 (s), 1480 (m), 1276 (m), 815 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.02–6.90 (m, 10H, 2 x C_6H_5), 5.86 (d, 1H, *J* = 6.30 Hz, C_3H), 5.00 (br,s, 2H, NH_2, exchanged in D_2O), 3.50 (dt, 2H, *J* = 6.74, 6.06 Hz, C_3' 2H), 3.38 (br,s,1H, NHC_6H_5), 2.70 (dt, 1H, *J* = 7.20, 6.18 Hz,C_4H), 1.52–1.28 (m, 4H); ^{13}C NMR($CDCl_3$): δ 137.21, 135.44, 134.00, 133.10, 130.66, 129.40, 128.32, 127.84 (aromatic carbons), 86.94 (C_5/$C_{2'}$), 74.24 (C_3), 55.70 (C_4), 27.87, 25.63, 24.00 (3',4',5' CH_2 carbons); MS (*m/z*): 311 (M^+), 295, 218, 203 (B.P), 202, 92, 77; HRMS-EI: Calcd for $C_{18}H_{21}O_2N_3$ (M), 311.2054. Found: M^+, 311.2037.

(S)-3-phenyl-(3S,4S,5S)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiroisoxazole (**7**): Colourless gummy liquid. Yield 78%, R_f = 0.52; IR (KBr): 3040 (m), 2965 (m), 1760 (s), 1685 (m), 1464 (s), 1290 (m), 1084 (s), 808 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.81(s,5H,C_6H_5), 4.67 (s, 1H, $NHCH_3$), 3.36 (s, 6H, 2 x N-CH_3), 3.00 (d, 1H, *J* = 5.74 Hz, C_3H), 2.74 (dt, 1H, *J* = 6.64, 6.30 Hz, C_4H), 2.30 (dt, 2H, *J* = 5.10, 4.92 Hz, C_3'2H), 1.80–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 129.05, 128.53, 128.27, 127.22 (aromatic carbons), 80.28 (C_5/$C_{2'}$), 70.36 (C_3), 59.70 (C_4), 45.17 (N-CH_3), 41.64 (NH-CH_3), 32.07, 31.22, 29.34 (3',4',5'CH_2 carbons); MS (*m/z*):248 (M^+), 218, 171, 156 (B.P), 141, 77. HRMS-EI: Calcd for $C_{14}H_{20}O_2N_2$ (M), 248.1862. Found: M^+, 248.1853.

(S)-3-Phenyl-(3S,4S,5S)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiroisoxazole (**8**): Colourless gummy liquid. Yield 78%, R_f = 0.48; IR (KBr): 3024 (m), 2950 (m), 1772 (s), 1670 (s), 1468 (m), 1382 (m), 805 (m), 780 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.50–6.62 (m, 15H, 3 x C_6H_5), 5.84 (s,1H, NHC_6H_5), 4.63 (d, 1H, *J* = 6.06 Hz, C_3H), 4.02 (dt, 1H, *J* = 6.18, 6.20 Hz, C_4H), 2.64 (dt, 2H, *J* = 5.28, 4.10 Hz,C_3'2H), 2.00–1.26 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 136.76, 136.53, 136.24, 135.15, 134.90, 134.62, 134.30, 133.78, 132.44, 132.18, 130.92, 130.37 (aromatic carbons), 83.22 (C_5/$C_{2'}$), 71.52 (C_3), 52.89 (C_4), 23.61, 22.57, 21.14 (3',4',5' CH_2 carbons); MS (*m/z*): 372 (M^+), 295, 280, 218, 203 (B.P), 92, 77; HRMS-EI: Calcd for $C_{24}H_{24}O_2N_2$ (M), 372.2286. Found: M^+, 372.2270.

The authors thank Dr M.P Kharel, Principal, Sikkim Government College, Gangtok for providing facilities and constant encouragement. We are pleased to acknowledge the financial support from UGC, New Delhi (Grant no:34-304/2008-SR) and also to CDRI, Lucknow for providing spectral data.

Received 23 January 2010; accepted 27 February 2010
Paper 100976 doi: 10.3184/030823410X12675422347141
Published online: 22 March 2010

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