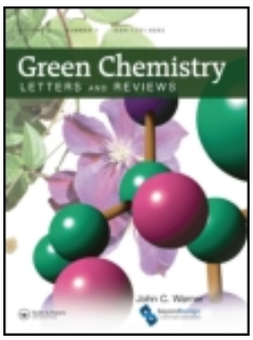


Green Chemistry Letters and Reviews

ISSN: 1751-8253 (Print) 1751-7192 (Online) Journal homepage: https://www.tandfonline.com/loi/tgcl20

Microwave-assisted synthesis of novel spiro isoxazolidine derivatives

Bhaskar Chakraborty , Prawin Kumar Sharma & Saurav Kafley

To cite this article: Bhaskar Chakraborty , Prawin Kumar Sharma & Saurav Kafley (2013) Microwave-assisted synthesis of novel spiro isoxazolidine derivatives, Green Chemistry Letters and Reviews, 6:2, 141-147, DOI: 10.1080/17518253.2012.720719

To link to this article: https://doi.org/10.1080/17518253.2012.720719

Published online: 19 Dec 2012.

Green Chemistry Letters and Reviews, 2013
Vol. 6, No. 2, 141–147, http://dx.doi.org/10.1080/17518253.2012.720719

Taylor & Francis
Taylor & Francis Group

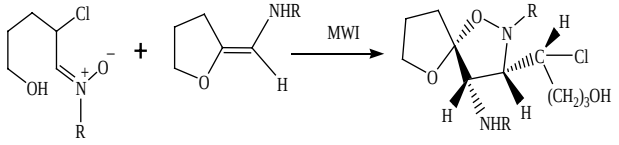
Microwave-assisted synthesis of novel spiro isoxazolidine derivatives

Bhaskar Chakraborty*, Prawin Kumar Sharma and Saurav Kafley

Organic Chemistry Laboratory, Department of Chemistry, Sikkim Government College, Sikkim University, Gangtok, Sikkim, India

(Received 29 June 2011; final version received 2 August 2012)

α-*N*-substituted furan derivatives as new dipolarophiles have been employed in 1,3-dipolar cycloaddition reaction with α-chloro nitrones under microwave irradiation and found to afford exclusively novel regioselective 5-spiro cycloadducts with high yield in a very short reaction time.



Keywords: α-*N*-substituted furan derivatives; spiro isoxazolidines; regioselectivity; MWI

Introduction

The utility of nitrones in synthetic organic chemistry has been widely illustrated especially in the synthesis of various substituted isoxazolidine and isoxazolines [1–3]. Moreover, nitrones can be used as potential oxidizing reagents in the conversion of various alkyl halides to aldehydes and ketones with high yield [4–7]. They are also versatile intermediates for the synthesis of natural products and many biologically interesting molecules [1,8]. Owing to the labile nature of the N–O bond under mild reducing conditions, isoxazolidines provide easy access to a variety of fascinating 1,3-difunctional aminoalcohols [9,10]. Performing cycloaddition reaction with new dipolarophiles is always a demanding area in organic synthesis especially when the reaction is carried out in environment-friendly conditions. To meet this challenge we would like to introduce α-*N*-substituted furan derivatives as novel efficient dipolarophiles in this communication. Microwave irradiation can be used as a facile and general method for the construction of variety of isoxazolidine and isoxazoline derivatives where considerably shortened reaction time is involved and is considered as an important approach toward ''Green Chemistry'' because of its eco-friendly nature [11–13]. In continuation of our environment-friendly synthesis of isoxazolidine, isoxazoline derivatives in solid phase and in hydrated media [14–17], we report herein synthesis of some novel 5-substituted spiro cycloadducts using α-*N*-substituted furan derivatives as dipolarophile with α-chloro nitrones under microwave irradiation with an excellent yield (Scheme 1, Table 1).

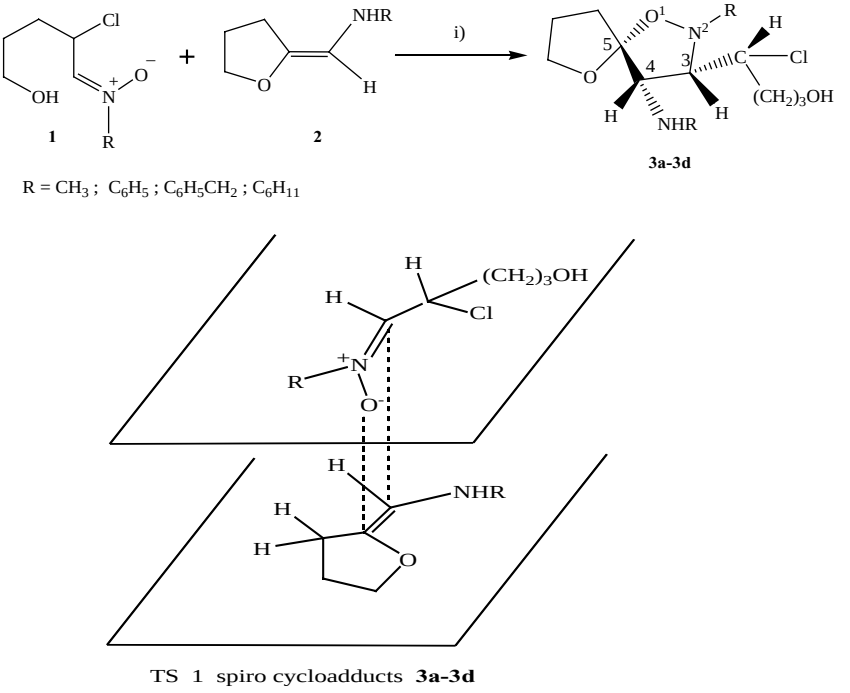
Results and discussion

α-*N*-substituted furan derivatives were obtained as side products during aldehyde and ketone synthesis from various alkyl halides using α-chloro nitrones as potential oxidizing reagents (Scheme 2) [4,6,7].

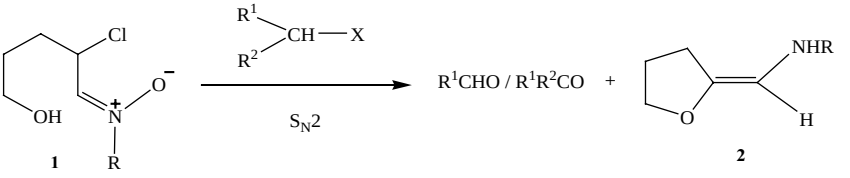
A new approach in the synthesis of α-chloro nitrones (**1: R = Me, Ph, $PhCH_2$, Cy**) from dihydropyran via chlorohydrine has been already reported (Scheme 3) [17].

Initially, we surveyed the reactions in conventional methods but in terms of reaction rate, yield, and greener approach our group was encouraged by the microwave technology. The cycloaddition reaction of α-chloro nitrones (**1: R = Me, Ph, $PhCH_2$, Cy**) [7,10,17] with α-*N*-substituted furan derivatives are much faster (5–10 min) under microwave irradiation compared with conventional methods (8–12 hr). All the furan derivatives (**2**) reacted very well with different α-chloro nitrones (**1**) in reaction conditions mentioned in Table 1. The reaction of nitrone **1** with furan derivatives **2** as dipolarophile are found to be highly regioselective to form solely 5-spiro isoxazolidine derivatives (**3a–3d**) [18–20]. It could be due to the fact that nitrone (lowest unoccupied molecular

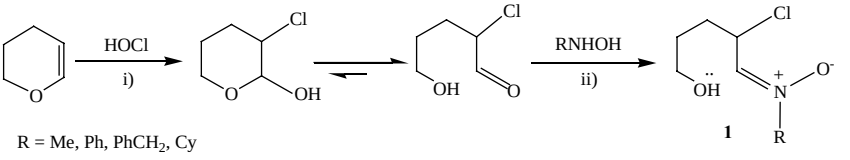
*Corresponding author. Email: bhaskargtk@yahoo.com



Scheme 1. Microwave-assisted synthesis of novel spiro isoxazolidines.
Reaction condition: (i) MWI, DMF (2 mL), 5–10 min, 34–40°C.



Scheme 2. Synthesis of *N*-substituted furan derivatives.
R = Me; Ph; PhCH2; Cy R1 = Me; Et; Pr; Ph; R2 = H; Me; Et; Ph X = C l, Br, I.



Scheme 3. Synthesis of alfa chloro nitrones.
R = Me, Ph, PhCH2, Cy.
Reaction conditions: (i) RT, N_2 atmosphere, 8 hr. (ii) RT, N_2 atmosphere, dry ether, anhydrous MgSO4, 10 hr.

orbital [LUMO]) – dipolarophile (highest occupied molecular orbital [HOMO]) interactions are strong enough to dominate the reaction and leads to the formation of solely 5-spiro isoxazolidines via an *exo* approach of nitrone **1** (in *Z* configuration) to the furan derivatives **2** (transition state **1**) [20].

A preferential conformation for the spiro regioselective isoxazolidine derivatives (**3a–3d**) may be represented in Figure 1.

We have also successfully tested these reactions in large scale (taking 6 mmols of nitrone and dipolarophiles) following conventional methodology as far as the feasibility and process chemistry of these reactions are concerned (respective yields are mentioned in Experimental section). The stereochemistry of the spiro isoxazolidine derivatives **3a–3d** was rationalized by considering multiplicity of the proton signals at 3-H, 4-H, CHCl asymmetric centers along with their coupling constant values [21,22]. Prominent double doublet signals for H-3 protons were obtained in all the novel spiro cycloadducts while H-4 protons appeared as doublet. NH protons of NHR

Table 1. Physical characteristics of the spiro cycloadducts (**3a–3d**).

Entry	Nitrone	Dipolarophile[a]	Nature of spiro cycloadduct[b]	Time (minute)	Yield[c] (%)
1	R = Me	α-*N*-methyl furan derivative	3a: Yellow gummy liquid	5	96 (88)
2	R = Ph	α-*N*-phenyl furan derivative	3b: Red viscous liquid	6	95 (86)
3	R = $PhCH_2$	α-*N*-benzyl furan derivative	3c: Red gummy liquid	8	93 (78)
4	R = Cy	α-*N*-cyclohexyl furan derivative	3d: Dark red liquid	10	93 (72)

[a]Reaction condition: α-chloro nitrone (1 mmol), dipolarophile (1 equivalent), dry DMF, MWI, 34–40°C.
[b]All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS spectral data.
[c]Isolated yields after purification. Figures in the parenthesis indicate reactions performed in conventional methods.

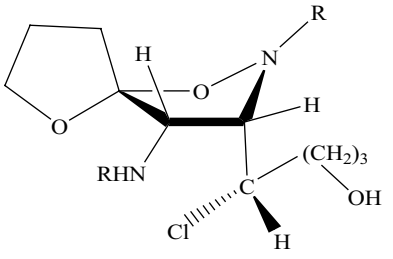


Figure 1. General conformation for the spiro cycloadducts (**3a–3d).**

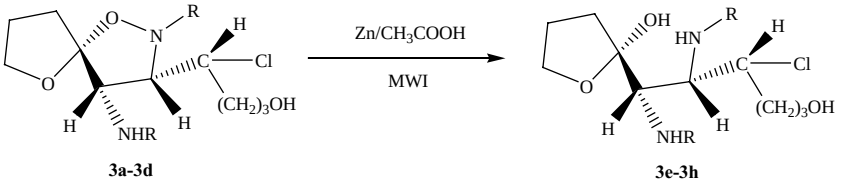
substituent of all the products were obtained as broad singlets while CHCl protons appeared as doublet of triplets. In all the spiro cycloadducts, the methylene protons of furan ring, butanol substituent, and cyclohexyl groups are merged and appeared as multiplets. In the ^{1}H NMR spectrum of spiro cycloadducts **3a–3d**, 3-H resonates around δ_H 2.50–4.28 ppm while 4-H around δ_H 3.00–3.96 ppm and the average coupling constant is $J_{3,4} \sim 7.16$ Hz implying a *cis* relationship between H-3 and H-4. The CHCl proton also resonates upfield around δ_H 2.35 ppm. The 3-H and CHCl protons are also *syn* as evidenced from their coupling constant values ($J_{3,CHCl} \sim 6.20$ Hz) [21,22]. Cycloaddition of *Z* nitrone via *exo*-transition state geometry results *syn* spiro isoxazolidine derivatives. In the mass spectrum, significant $M^+ + 2$ ion peak of characteristic heights are obtained in the regioselective spiro cycloadducts as the peak of highest *m*/*z* value due to isotopic abundance of Cl^{37} atoms in these compounds. Studies of HRMS spectra show almost exact mass for the majority of the compounds.

Furthermore, the synthetic potentiality of the new spiro cycloadducts are tremendous as they could be easily converted into corresponding spiro 1,3 amino alcohol derivatives readily upon treatment with Zn and CH_3COOH under microwave irradiation [23–26]. Studies are in progress. In addition, all the new spirocycles have shown potential antibacterial activities. A proposal for patenting α-*N*-substituted furan derivatives employed in the present study is underway.

In summary, we have described the use of α-*N*-substituted furan derivatives as efficient dipolarophiles in the cycloaddition reactions for the synthesis of novel regioselective cycloadducts. All the reactions are successfully carried out under microwave irradiation with very high yield in a very short reaction time and with high selectivity. The products can also be successfully transformed into spiro 1,3 amino alcohols under microwave irradiation and may find importance in organic synthesis. Further applications of these new products are underway in our laboratory and will be reported in the near future. Therefore, it is believed that the procedure described here may be applied in the synthesis of other new spiro isoxazolidine derivatives like α-*N*-butyl/*p*-methoxy phenyl furan derivatives, etc., as efficient dipolarophiles and thereby offering greater scope in cycloaddition reactions.

Experimental

^{1}H NMR spectra were recorded with a Bruker DRX 300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded



Scheme 4. Synthesis of amino alcohols from spiro isoxazolidines.
R = Me; Ph; PhCH2; Cy
Reaction condition: MWI, 8 min, 30°C.

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 machine 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 DART–HRMS, JMS–T100LC, Accu-TOF instrument. All the reactions were monitored by thin layer chromatography (TLC) using 0.25 mm silica gel plates (Merck $60F_{254}$ UV indicator) while column chromatography was performed with silica gel (E. Merck India) 60–200 mesh. Optical rotations $[\alpha]_D^{24}$ were measured on Equip-Tronics EQ-800 digital polarimeter at 24°C in $CHCl_3$. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-methylhydroxylamine, *N*-benzylhydroxylamine were purchased from Aldrich Chemical Company and were used as received. *N*-phenylhydroxylamine and *N*-cyclohexylhydroxylamine [27] were prepared following standard methods available in the literature and have been used already for the synthesis of aldehydes/ketones and cycloaddition reactions involving α-amino, α-chloro nitrones in aqueous phase and in solvent-free conditions. Microwave studies were carried out in Discover Bench Mate system (Make: CEM-USA) producing continuous irradiation at 2445 MHz and infrared control system. Microwave experiments were carried out in open vessels with an effective magnetic stirring and reflux (which avoids all problems of nonhomogeneity in temperature).

General procedure for the synthesis of spiro isoxazolidines (3a–3d) (conventional)

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 α-*N*-methyl furan derivative [(*E*)-1-(dihydrofuran-2-(3*H*)-ylidene)-*N*-methyl methanamine)] (1 equivalent) and was stirred at room temperature (RT) with a magnetic stirrer under N_2 atmosphere for 4 hr. 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 vacuum pump and finally purified by column chromatography using ethyl acetate–hexane to afford pure spiro cycloadduct **3a** (entry 1, Table 1, Scheme 1). This procedure was followed for the reaction of other α-chloro nitrones (**R = Ph, $PhCH_2$, Cy**) with furan derivatives **2** listed in Table 1. As we have found more faster reaction rates and better yields in microwave irradiated reactions, therefore we discarded this conventional methodology.

General procedure for the synthesis of spiro isoxazolidines (3a–3d) in large scale (conventional)

To a well-stirred solution of nitrone **1** (**R = Me**; 6.06 mmole) in diethyl ether (25 mL) taken in a 50-mL conical flask was added α-*N*-methyl furan derivative [(*E*)-1-(dihydrofuran-2-(3*H*)-ylidene)-*N*-methyl methanamine)] (1 equivalent) and was stirred at RT with a magnetic stirrer under N_2 atmosphere for 10 hr. 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 vacuum pump and finally purified by column chromatography using ethyl acetate–hexane to afford pure spiro cycloadduct **3a** (82%, entry 1, Table 1, Scheme 1). This procedure was tested for the feasibility of the reactions with other α-chloro nitrones (**R = Ph, $PhCH_2$, Cy**) and furan derivatives **2** listed in Table 1 (respective yield: for **R = Ph**, 74%; **R = $PhCH_2$**, 70%; **R = Cy**, 68%).

General procedure for the synthesis of spiro isoxazolidines (3a–3d) (microwave)

To a solution of nitrone **1** (**R = Me**; 1 mmole) in dry DMF (2 mL), [(*E*)-1-(dihydrofuran-2-(3*H*)-ylidene)-*N*-methyl methanamine) **2**] (1 equivalent) was added and after shaking the reaction mixture was irradiated for 5 min at 34°C. The completion of reaction was monitored by TLC ($R_f = 0.53$). The reaction mixture was cooled to RT and poured into crushed ice. The reaction mass was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to obtain the crude product. Pure product (**3a**) was obtained by column chromatography over silica gel (entry 1, Table 1, Scheme 1). This procedure was followed for the reaction of other α-chloro nitrones (**R = Ph, $PhCH_2$, Cy**) with furan derivatives **2** listed in Table 1.

Spectral and physical data of the new compounds were found as follows:

(*S*)-4-chloro-4-((3*S*,4*S*,5*S*)-2-methyl-4-(methylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol (3a)

Dark yellow viscous liquid; Yield 96%; $R_f = 0.53$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: +26.06° (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.83$ (br, 1*H*, CH_2OH, exchanged in D_2O), 4.50 (br, s, 1*H*, $NHCH_3$), 3.31 (s, 6*H*, 2 × N–CH_3), 2.99 (d, 1*H*, $J = 7.16$ Hz, C_4H), 2.50 (dd, 1*H*, $J = 6.06$, 6.10 Hz, C_3H), 2.19 (dt, 1*H*, $J = 6.46$, 6.50 Hz, CHCl), 1.66 – 1.60 (m, 12*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 93.00$ (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 (FAB): m/z 280 ($M^+ + 2$), 278 (M^+), 263, 248, 156 (BP), 141, 107.

HRMS (ESI): m/z calculated for $C_{12}H_{23}O_3N_2Cl$: 278.1570; found: 278.1536.

IR (KBr): υ_{max} 3480 (s), 3460–3326 (br), 2948 (m), 2420 (m), 1485 (s), 1376 (m), 1236 (s), 810 (m), 774 (s) cm^{-1}.

(*S*)-4-chloro-4-((3*S*,4*S*,5*S*)-2-phenyl-4-(phenylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol (3b)

Yellow gummy liquid; Yield 95%; $R_f = 0.48$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: +23.07° (*c*, 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.98$–6.93 (m, 10*H*, 2 × C_6H_5), 5.84 (d, 1*H*, $J = 7.20$ Hz, C_4H), 4.96 (br, 1*H*, CH_2OH, exchanged in D_2O), 3.51 (dd, 1*H*, $J = 7.34$, 7.38 Hz, C_3H), 3.45 (br, s, 1*H*, NHPh), 2.61 (dt, 1*H*, $J = 6.44$, 6.42 Hz, CHCl), 1.88–1.15 (m, 12*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.00$, 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 (FAB): m/z 404 ($M^+ + 2$), 402 (M^+), 325, 310, 309, 218 (BP), 107, 91, 77.

HRMS (ESI): m/z calculated for $C_{22}H_{27}O_3N_2Cl$: 402.1850, found: 402.1744.

IR (KBr): υ_{max} 3476 (s), 3465 – 3290 (br), 3050 (m), 2425 (m), 1620 (s), 1380 (s), 1240 (m), 1040 (m), 780 (s) cm^{-1}.

(*S*)-4-chloro-4-((3*S*,4*S*,5*S*)-2-benzyl-4-(benzylamino)-1,6-dioxa-2-azaspiro[4.4]nonan-3-yl)butan-1-ol (3c)

Red gummy liquid; Yield 93%; $R_f = 0.46$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: +18.02° (*c*, 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.18$–6.90 (m, 10*H*, 2 × C_6H_5), 5.05 (br, 1*H*, CH_2OH, exchanged in D_2O), 4.80 (s, 2*H*, –NCH_2Ph), 3.73 (d, 1*H*, $J = 7.20$ Hz, C_4H), 3.36 (dd, 1*H*, $J = 6.10$, 6.15 Hz, C_3H), 3.22 (s, 2*H*, –$NHCH_2Ph$), 2.60 (dt, 1*H*, $J = 6.06$, 6.00 Hz, CHCl), 2.24 (br, s, 1*H*, $NHCH_2Ph$), 1.44–1.18 (m, 12*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 137.23$, 136.90, 135.67, 135.12, 131.66, 130.75, 130.22, 128.86 (aromatic carbons), 96.54 (CHCl), 83.42 (C_5), 75.20 (C_3), 54.27 (C_4), 35.60, 35.24 (benzyl carbons), 26.77, 26.16, 24.00, 23.70, 23.15, 21.60 (6 CH_2 carbons).

MS (FAB): m/z 432 ($M^+ + 2$), 430 (M^+), 339, 323, 232 (BP), 107, 106, 91, 77.

HRMS (ESI): m/z calculated for $C_{24}H_{31}O_3N_2Cl$: 430.2190, found: 430.2168.

IR (KBr): υ_{max} 3580–3510 (br),3472 (m), 2430 (m), 1626 (s),1383 (s), 1230 (m), 1100 (m),780 (s) cm^{-1}.

(*S*)-4-chloro-4-((3*S*,4*S*,5*S*)-2-cyclohexyl-4-(cyclohexylamino)-1,6-dioxa-2-azaspiro[4.4] nonan-3-yl)butan-1-ol (3d)

Dark red liquid; Yield 93%; $R_f = 0.50$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: +12.08° (*c*, 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.23$ (br, 1*H*, CH_2OH, exchanged in D_2O), 4.28 (dd, 1*H*, $J = 6.80$, 6.85 Hz, C_3H), 3.96 (d, 1*H*, $J = 6.26$ Hz, C_4H), 3.54 (br, s, 1*H*, N–H proton of NHC_6H_{11}), 2.74 (dt, 1*H*, $J = 7.44$, 7.50 Hz, CHCl), 1.92–1.16 (m, 34*H*, cyclohexyl and methylene protons).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 90.50$ (CHCl), 88.10 (C_5), 73.07 (C_3), 55.60 (C_4), 36.66, 32.50, 32.12, 31.20, 29.76, 29.30, 28.68, 28.25, 27.35, 27.18, 26.93, 24.80, 24.16, 23.92, 22.74, 22.17, 20.33, 20.12 (18 CH_2 carbons).

MS (FAB): m/z 416 ($M^+ + 2$), 414 (M^+), 331, 315, 224 (BP), 107, 98, 83.

HRMS (ESI): m/z calculated for $C_{22}H_{39}O_3N_2Cl$: 414.2670, found: 414.2644.

IR (KBr): υ_{max} 3610–3540 (br), 3465 (m), 2432 (m), 1624 (s), 1485 (s), 1366 (m), 1235 (m), 770 (s) cm^{-1}.

Table 2. Physical characteristics of the amino alcohols (**3e–3h**).

Entry	Spiro isoxazolidines	Reagent[a]	Nature of amino alcohol[b]	Time (minute)	Yield[c] (%)
1	**3a**	Zn/CH_3COOH	**3e**: Pale Yellow liquid	8 (2hr)	83 (64)
2	**3b**	Zn/CH_3COOH	**3f**: Brown thick liquid	9 (3 hr)	80 (61)
3	**3c**	Zn/CH_3COOH	**3g**: Gray liquid	8 (3 hr)	76 (58)
4	**3d**	Zn/CH_3COOH	**3h**: Red liquid	9 (3 hr)	76 (56)

[a]Reaction condition: Spiro isoxazolidines (1 mmol), Zn (5 mg), CH_3COOH (3.5 ml), MWI, 34–40°C.
[b]All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS spectral data.
[c]Isolated yields after purification. Figures in the parenthesis indicate reactions performed in conventional methods.

General procedure for synthesis of amino alcohols (3e–3h) (conventional)

A mixture of spiro isoxazolidine **3a** (R = Me; 1 mmole), Zn dust (5 mg), glacial acetic acid (7 mL) was taken in a 20-mL conical flask and the reaction mixture was stirred with a magnetic stirrer under N_2 atmosphere for 2 hr at 60°C. The completion of reaction was monitored by TLC ($R_f = 0.66$). The reaction mixture was cooled to RT and filtered. Excess acetic acid in the filtrate was removed through basic work-up and finally column chromatographic purification result 1,3 amino alcohol (**3e**) in 64% yield. This procedure was followed with other spiro isoxazolidines (**3b–3d**) listed in Table 2 and the figures in parentheses indicate yield. As we have found more faster reaction rates and better yields in microwave irradiated reactions, therefore we discarded this conventional methodology.

General procedure for synthesis of amino alcohols (3e–3h) (microwave)

To a mixture of spiro isoxazolidine **3a** (R = Me; 1 mmole) and Zn dust (5 mg), glacial acetic acid (3.5 mL) was added and after shaking the reaction mixture was irradiated for 8 min at 30°C. The completion of reaction was monitored by TLC ($R_f = 0.66$). The reaction mixture was cooled to RT and filtered. Excess acetic acid in the filtrate was removed through basic work-up and finally column chromatographic purification result desired spiro 1,3 amino alcohol (**3e**) in 83% yield. This procedure was followed with other spiro isoxazolidines (**3b–3d**) listed in Table 2.

(*S*)-2-((*1S,2S,3S*)-3-chloro-6-hydroxy-1,2-*bis* (methylamino)hexyl)-tetrahydrofuran-2-ol (3e)

Yellow liquid; Yield 83%; $R_f = 0.66$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: +103.08° (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.30$ (br, 1*H*, CH_2OH, exchanged in D_2O), 4.83 (br, 1*H*, CH_2OH, exchanged in D_2O), 4.37 (br, s, $2 \times 1H$, $NHCH_3$), 3.24 (s, 6*H*, $2 \times N–CH_3$), 3.10 (d, 1*H*, $J = 4.06$ Hz, C_2H), 2.76 (dd, 1*H*, $J = 3.38$, 3.28 Hz, C_1H), 2.44 (dt, 1*H*, $J = 2.20$, 2.22 Hz, CHCl), 1.95–1.34 (m, 12*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 97.30$ (CHCl), 80.64 (C_1), 75.78 (C_2), 60.26 ($C_{2'}$), 50.62, 50. 42 (N–CH_3 carbons), 27.17, 26.54, 26.10, 24.90, 24.52, 23.77 (6 CH_2 carbons).

MS (FAB): *m/z* 282 ($M^+ + 2$), 280 (M^+), 145, 107.

HRMS (ESI): *m/z* calculated for $C_{12}H_{25}O_3N_2Cl$: 280.1710; found: 280.1675.

IR (KBr): υ_{max} 3660–3585 (br), 3530–3495 (br), 3470 (m), 1480 (s), 1376 (m), 1232 (s), 816 (m), 770 (s) cm^{-1}.

(*S*)-2-((1*S*,2*S*,3*R*)-3-chloro-6-hydroxy-1,2-bis (phenylamino)hexyl)-tetrahydrofuran-2-ol (3f)

Brown thick liquid; Yield 80%; $R_f = 0.70$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: +94.22° (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.64–7.27$ (m, 10*H*, aromatic protons), 5.24 (br, 1*H*, CH_2OH, exchanged in D_2O), 5.02 (br, 1*H*, CH_2OH, exchanged in D_2O), 4.68 (br, s, $2 \times 1H$, NHC_6H_5), 3.34 (d, 1*H*, $J = 3.68$ Hz, C_2H), 2.90 (dd, 1*H*, $J = 5.20$, 5.16 Hz, C_1H), 2.50 (dt, 1*H*, $J = 4.40$, 4.12 Hz, CHCl), 2.05–1.63 (m, 12*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 136.78$, 134.90, 134.53, 133.97, 131.80, 131.14, 130.45, 130.08 (aromatic carbons), 94.55 (CHCl), 84.10 (C_1), 78.40 (C_2), 61.27 ($C_{2'}$), 25.60, 25.12, 24.45, 23.88, 23.32, 22.13 (6 CH_2 carbons).

MS (FAB): *m/z* 406 ($M^+ + 2$), 404 (M^+), 308, 296, 205, 107, 77.

HRMS (ESI): *m/z* calculated for $C_{22}H_{29}O_3N_2Cl$: 404.2360; found: 404.2332.

IR (KBr): υ_{max} 3620–3555 (br), 3515–3476 (br), 3310 (m), 2850 (m), 1460 (s), 1365 (s), 825 (m), 776 (s) cm^{-1}.

(*S*)-2-((1*S*,2*S*,3*R*)-1,2-*bis*(benzylamino)-3-chloro-6-hydroxyhexyl)-tetrahydrofuran-2-ol (3g)

Gray liquid; Yield 76%; $R_f = 0.68$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: −54.23° (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.70–7.28$ (m, 10*H*, aromatic protons), 5.12 (br, 1*H*, CH_2OH, exchanged in D_2O), 4.95 (br, 1*H*, CH_2OH, exchanged in D_2O), 4.60 (br, s, $2 \times 1H$, NHC_6H_5), 4.22 (s, $2 \times 2H$, $CH_2C_6H_5$), 3.72 (d, 1*H*, $J = 3.80$ Hz, C_2H), 3.18 (dd, 1*H*, $J = 4.12$, 4.00 Hz, C_1H), 2.64 (dt, 1*H*, $J = 3.50$, 3.44 Hz, CHCl), 2.26–1.80 (m, 12*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 135.06$, 134.85, 133.46, 133.13, 132.30, 130.55, 130.14, 130.04 (aromatic carbons), 92.70 (CHCl), 82.12 (C_1), 74.50 (C_2), 60.28 ($C_{2'}$), 32.87, 30.42 (benzyl carbons), 24.33, 24.14, 22.47, 21.56, 21.10, 20.64 (6 CH_2 carbons).

MS (FAB): *m/z* 434 ($M^+ + 2$), 432 (M^+), 325, 234, 219, 107, 106, 91.

HRMS (ESI): *m/z* calculated for $C_{24}H_{33}O_3N_2Cl$: 432.2660; found: 432.2625.

IR (KBr): υ_{max} 3610–3540 (br), 3530–3480 (br), 2855 (m), 1465 (s), 1362 (s), 840 (m), 784 (s) cm^{-1}.

(*S*)-2-((1*S*,2*S*,3*S*)-3-chloro-1,2-*bis*(cyclohexylamino)-6-hydroxyhexyl)-tetrahydrofuran-2-ol (3h)

Red liquid; Yield 76%; $R_f = 0.66$ (hexane–ethyl acetate, 5:1); $[\alpha]_D^{24}$: -38.90° (*c* 1.00, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.08$ (br, 1*H*, CH_2OH, exchanged in D_2O), 4.93 (br, 1*H*, CH_2OH, exchanged in D_2O), 4.70 (br, s, $2 \times 1H$, NHC_6H_{11}), 3.60 (d, 1*H*, $J = 2.55$ Hz, C_2H), 2.95 (dd, 1*H*, $J =$ 3.80, 3.74 Hz, C_1H), 2.44 (dt, 1*H*, $J = 2.30$, 2.26 Hz, CHCl), 2.30–1.46 (m, 34*H*).

^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 95.15$ (CHCl), 82.45 (C_1), 73.44 (C_2), 61.30 ($C_{2'}$), 26.10, 26.04, 25.90, 25.77, 25.52, 25.37, 23.88, 23.54, 23.26, 23.08, 22.55, 22.18, 20.65, 20.32, 20.16, 19.62, 19.40, 19.15 (cyclohexyl and other methylene CH_2 carbons).

MS (FAB): *m*/*z* 418 ($M^+ + 2$), 416 (M^+), 333, 309, 226, 211, 107, 83.

HRMS (ESI): *m*/*z* calculated for $C_{22}H_{41}O_3N_2Cl$: 416.3200; found: 416.3178.

IR (KBr): υ_{max} 3605–3530 (br), 3510–3464 (br), 3290 (m), 2840 (s), 1440 (s), 1260 (m), 960 (s) cm^{-1}.

Acknowledgements

Financial support from University Grants Commission, New Delhi (grant no:34-304/2008-SR) is gratefully acknowledged. We are also grateful to Dr M.P. Kharel, Principal, Sikkim Government College for providing facilities and also to Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow for providing spectral data.

References

[1] Padwa A, Pearson WH. Synthetic application of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products. New Jersey: Wiley; 2003.
[2] Kobayashi S, Jørgensen KA. Cycloaddition reactions in organic synthesis. Weinheim: Wiley-VCH; 2002.
[3] Huisgen R, Padwa A, editors. 1,3-dipolar cycloaddition chemistry. Vols. 1 and 2. New York: Wiley-Interscience; 1984.
[4] Chakraborty B, Sharma PK, Kafley S, Chhetri MS, Ghosh AR. J Ind Chem Soc. 2011;88:245–250.
[5] Chakraborty B, Chhetri MS, Rai N, Sharma PK. J Ind Chem Soc. 2010;87:1399–1404.
[6] Chakraborty B, Chhetri MS. Indian J Chem. 2008;47B:485–488.
[7] Chakraborty B, Sharma PK. Synth Commun. 2012;42:1804–1812.
[8] Gothelf KV, Jorgensen KA. Chem Rev. 1998;98:863–872.
[9] Frederickson M. Tetrahedron. 1997;53:403–408.
[10] Chakraborty B, Sharma PK. Indian J Chem Sect B. 2012;51B:1145–1150.
[11] Etiemey JP, Lidstrom P. Microwave assisted organic synthesis. Oxford: Blackwell publishing LTD; 2005.
[12] Loupy A. Microwaves in organic synthesis. Weinheim: Wiley-VCH; 2002, 2006.
[13] Alvareg HM, Loupy A, Caldron O, Periz E. Tetrahedron. 2006;62:2616–2619.
[14] Chakraborty B, Kafley S, Chhetri MS, Samanta A. Indian J Chem. 2010;49B:209–215.
[15] Chakraborty B, Chhetri MS. Indian J Chem. 2010;49B:102–106, 394.
[16] Chakraborty B, Chhetri MS, Samanta A. Indian J. Chem. 2010;49B:1155–1160.
[17] Chakraborty B, Sharma PK, Chhetri MS. J Heterocyclic Chem (Wiley). 2012;49(5):1260–1265.
[18] Newton R, Savage PG. Australian J Chem. 2008;61;432–438.
[19] Aouadik K, Vidal S, Praly PJ. Synlett. 2006;19:3299–3303.
[20] Houk KN, Sims J, Luskus CRJ. Am Chem Soc. 1973;95:7302–7307.
[21] Deshong P, Li W, Kennington JW, Ammon HLJ. Org Chem. 1991;56:1364–1369.
[22] Gandolfi R, Grunanger P. *The chemistry of the heterocyclic compounds*. Vol. 49. New York: Wiley Interscience; 1999, p. 774–791.
[23] Hoffman WR, Eichler G, Endesfelder A. Liebigs Ann. Chem. 1983;2000–2007.
[24] Yepez AF, Palma A, Stashenko E, Bahsas A, Amaro-Luis JM. Tetrahedron Lett. 2006;47:5825–5829.
[25] Merino P, Franco S, Marchan FL, Tejero T, Tetrahedron Asymmetry. 1997;8:3489–3493.
[26] Lait SM, Rankit DA, Keay BA. Chem Rev. 2007;107:767–776.
[27] Ghosh AR. Indian J Chem. 1984;23B:449–450.