

An Atom-economic and Facile Synthesis of Novel 4-Imino-3-phenyl-2-substitutedphenyl-5-tolyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxide through 1,3-Dipolar Cycloaddition Reactions

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Abstract

An atom economic and facile synthesis of novel thiadiazolidine-1-oxides has been achieved *via* using 1,3-dipolar cycloaddition reactions. The salient features of synthetic procedure are characterized by the good yields, high regio- and stereoselectivity, one-pot procedure, and operational simplicity. The regiochemistry and structures of the cycloadducts were determined by using various spectroscopic techniques (IR, ¹H-NMR, ESI-MS) and elemental analyses data.

Keywords: Atom-economic; Thiadiazolidine; Stereoselectivity; Antiparasitic; Antiviral; Cycloaddition

Introduction

Organic synthesis has been one of the most successful scientific disciplines, and has also been of enormous practical utility. In the course of few last years, the progress of organic synthesis has been manifold and has gained importance in the field of heterocyclic compounds. This synthetic organic chemistry provides cornucopia of heterocyclic systems. Among various synthetic methods, cycloaddition reactions involving two simple components appear to be an attractive choice for the stereoselective synthesis of heterocyclic compounds due to its atom-economic and facile nature. Compounds incorporating heterocyclic ring systems continue to attract considerable interest due to the wide range of biological activities they possess. Amongst them, five-membered heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. Five-membered heterocycles like thiadiazolidine have found wide applications in the fields of pharmaceutical chemistry and have stimulated much interest in the field of medicinal and biological chemistry. The value of thiadiazolidine derivatives is significant among various heterocycles, as they are found to possess antibacterial [1-4], anti-inflammatory [5,6], antiviral [7], antiparasitic [8], antifungal [9-11] and other diverse biological activities [12]. Many thiadiazolidines are used for the production of anticonvulsant drugs [13,14] and in the treatment of depression also [15]. In addition to this, thiadiazolidine derivatives have played a crucial role in the theoretical development of heterocyclic chemistry and are also used extensively in organic synthesis.

Encouraged by the diverse biological activities of thiadiazolidine substituted compounds, in our investigation we found an interesting approach to synthesize these substituted ring systems.

Experimental

General

Unless otherwise indicated, all common reagents were used as obtained from commercial suppliers (Sigma Aldrich) without further purification and the solvents were dried before use. All melting points were recorded on Gallen-Kamp apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RXIFT infrared spectrophotometer (manufactured at Buckinghamshire, England) using KBr pellets. ¹H-NMR, were recorded at 400 MHz on BRUKER spectrometer (manufactured at Fallanden, Switzerland) using tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Waters Micromass Q-T of Micro (ESI) spectrometer (manufactured at Vernon Hills, USA). Elemental analysis was carried

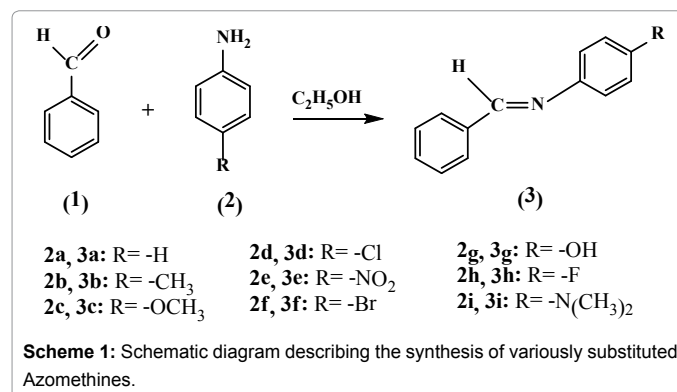
out using Elementar Vario MICRO cube CHN analyzer (Frankfurt, Germany). Thin-layer chromatography (TLC) analysis was carried out on glass plates coated with silica gel-G (Loba Chemie) suspended in methanol-chloroform. Column chromatography was performed using silica gel (60-120 mesh, Loba Chemie).

General procedure for the synthesis of substituted benzalaniline (3a-i)

The solution of benzaldehyde (0.01 mol) in ethanol (15 mL) taken in 100 mL beaker was added to the solution of substituted aniline (0.01 mol) in ethanol (15 mL) at room temperature. The reaction mixture was stirred for half an hour and then cooled in an ice bath for fifteen minutes (Scheme 1). The crude compound separated out was filtered at the suction pump and recrystallised from ethanol.

General procedure for the synthesis of *N*- α -cyano- α -phenyl methylaniline (4a-i)

To substituted benzalaniline (0.02 mol) taken in 250 mL conical



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flask were added ethanol (50 mL) and glacial acetic acid (5-6 mL). To this solution was added a solution of aqueous potassium cyanide (0.01 mol) in distilled water (10 mL) in small installments. The reaction mixture was stirred for one hour and then allowed to stay overnight (Scheme 2). On dilution with distilled water the crude product was separated out. The product was filtered, washed with distilled water and recrystallised from petroleum ether to give crystalline *N*- α -cyano- α -phenylmethylaniline.

General procedure for the synthesis of *N*-sulphonyl-4-toluidine (7)

A solution of pure thionyl chloride (0.69 mol) in 100 mL of anhydrous toluene was added slowly to a solution of recrystallised 4-toluidine in 250 mL of anhydrous benzene contained in a 1-litre capacity round bottomed flask with swirling motion and occasional cooling in ice-bath as the reaction was an exothermic one. Each successive addition of thionyl chloride solution was done only after the previous reaction had subsided. An immediate precipitation of toluidinium sulphonyl chloride occurs. After the addition of the thionyl chloride solution was complete, the mixture was heated to reflux using a calcium chloride guard tube on a heating mantle until a clear solution was obtained. Whole of the solid disappeared in about five hours and the reaction mixture was refluxed for another hour to complete the reaction (Scheme 3). The solvent and the excess of thionyl chloride were distilled off under reduced pressure to yield a yellow *N*-sulphonyl-4-toluidine.

General procedure for the synthesis of 4-imino-3-phenyl-2-substitutedphenyl-5-tolyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8a-i)

To the solution of *N*- α -cyano- α -phenylmethylaniline (0.01 mol) in anhydrous toluene taken in a 100 mL round bottomed flask were added few drops of triethylamine and *N*-sulphonyl-4-toluidine (0.01 mol) at room temperature. The reaction mixture after refluxing for 30-40 minutes was allowed to stand for overnight period. The reaction mixture on dilution with solvent ether gave the crude product (Scheme 4) which was subjected to column chromatography using hexane:ethyl acetate

(8:2) as an eluent to afford pure 4-imino-3-phenyl-2-substitutedphenyl-5-tolyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide derivatives 8a-i.

4-Imino-2-(4'-tolyl)-5-tolyl-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8a): Compound obtained as yellow solid; 68% yield; m.p. 116-118°C; IR (KBr pellets): 3329 cm⁻¹ (N-H); 1616 cm⁻¹ (C=N); 1590 cm⁻¹ (C=C); 1029 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.64-8.06 (m, 14H); δ 5.31 (s, 1H); δ 2.33 (s, 3H); δ 2.30 (s, 3H); MS(ESI): m/z 375[M⁺]; Anal. Calc. for C₂₂H₂₁N₃OS: C, 70.39; H, 5.59; N, 11.19; S, 8.52, Found: C, 70.42; H, 5.60; N, 11.20; S, 8.53.

2,3-Diphenyl-4-imino-5-tolyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8b): Compound obtained as yellow solid; 64% yield; m.p. 122-124°C; IR (KBr pellets): 3332 cm⁻¹ (N-H); 1622 cm⁻¹ (C=N); 1595 cm⁻¹ (C=C); 1024 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.62-8.03 (m, 14H); δ 5.30 (s, 1H); δ 2.30 (s, 3H); MS(ESI): m/z 361[M⁺]; Anal. Calc. for C₂₁H₁₉N₃OS: C, 69.80; H, 5.26; N, 11.63; S, 8.85, Found: C, 69.72; H, 5.25; N, 11.57; S, 8.86.

4-Imino-2-(4'-methoxyphenyl)-5-tolyl-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8c): Compound obtained as light yellow; 62% yield; m.p. 120-122°C; IR (KBr pellets): 3330 cm⁻¹ (N-H); 1620 cm⁻¹ (C=N); 1588 cm⁻¹ (C=C); 1030 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.70-8.10 (m, 14H); δ 5.40 (s, 1H); δ 3.67 (s, 3H); δ 2.34 (s, 3H); MS(ESI): m/z 391[M⁺]; Anal. Calc. for C₂₂H₂₁N₃O₂S: C, 67.51; H, 5.37; N, 10.74; S, 8.17, Found: C, 67.48; H, 5.36; N, 10.73; S, 8.18.

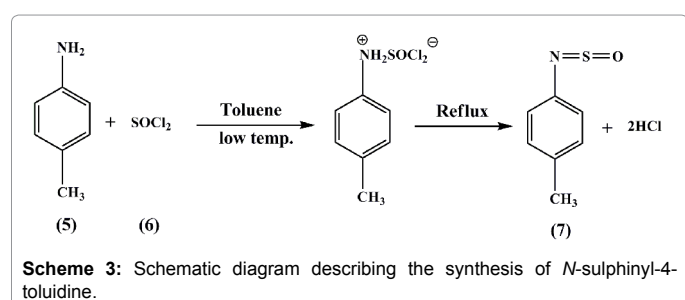
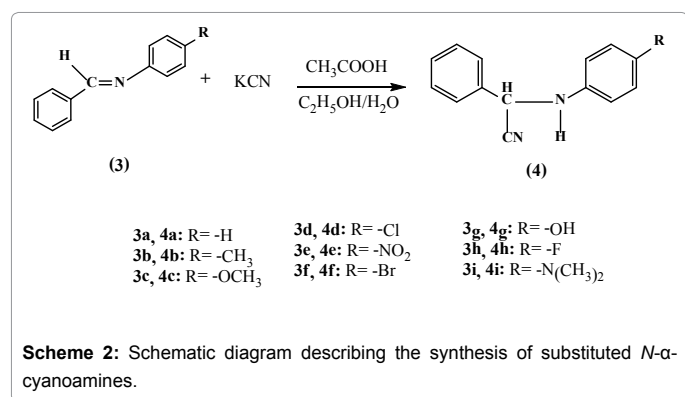
2-(4'-Chlorophenyl)-4-imino-5-tolyl-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8d): Compound obtained as light yellow solid; 70% yield; m.p. 102-104°C; IR (KBr pellets): 3325 cm⁻¹ (N-H); 1618 cm⁻¹ (C=N); 1595 cm⁻¹ (C=C); 1026 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.44-8.03 (m, 14H); δ 5.33 (s, 1H); δ 2.33 (s, 3H); MS(ESI): m/z 395 [M⁺], 397 [M⁺+2]; Anal. Calc. for C₂₁H₁₈ClN₃OS: C, 63.71; H, 4.55; N, 10.61; S, 8.08, Found: C, 63.69; H, 4.54; N, 10.60; S, 8.09.

4-Imino-5-tolyl-2-(4'-nitrophenyl)-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8e): Compound obtained as yellow solid, 65% yield, m.p. 154-156°C; IR (KBr pellets): 3330 cm⁻¹ (N-H); 1625 cm⁻¹ (C=N); 1587 cm⁻¹ (C=C); 1029 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.52-8.03 (m, 14H); δ 5.36 (s, 1H); δ 2.36 (s, 3H); MS(ESI): m/z 406[M⁺]; Anal. Calc. for C₂₁H₁₈N₄O₃S: C, 62.06; H, 4.43; N, 13.79; S, 7.87, Found: C, 62.08; H, 4.42; N, 13.78; S 7.88.

2-(4'-Bromophenyl)-4-imino-5-tolyl-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8f): Compound obtained as yellow solid; 72% yield, m.p. 114-116°C; IR (KBr pellets): 3320 cm⁻¹ (N-H); 1616 cm⁻¹ (C=N); 1592 cm⁻¹ (C=C); 1024 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.64-8.04 (m, 14H); δ 5.31 (s, 1H); δ 2.41 (s, 3H); MS(ESI): m/z 440 [M⁺], 442 [M⁺+2]; Anal. Calc. for C₂₁H₁₈BrN₃OS: C, 57.27; H, 4.09; N, 9.54; S, 7.26, Found: C, 57.25; H, 4.08; N, 9.53; S, 7.27.

2-(4'-Hydroxyphenyl)-4-imino-5-tolyl-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8g): Compound obtained as light yellow solid; 74% yield; m.p. 118-120°C; IR (KBr pellets): 3326 cm⁻¹ (N-H); 1612 cm⁻¹ (C=N); 1590 cm⁻¹ (C=C); 1029 cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 8.09 (s, 1H); 6.42-8.01 (m, 14H); δ 5.33 (s, 1H); δ 2.33 (s, 3H); MS(ESI): m/z 377 [M⁺]; Anal. Calc. for C₂₁H₁₉N₃O₂S: C, 66.84; H, 5.04; N, 11.14; S, 8.48, Found: C, 66.81; H, 5.03; N, 11.12; S, 8.49.

2-(4'-Fluorophenyl)-4-imino-5-tolyl-3-phenyl-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide (8h): Compound obtained as light yellow solid; 69% yield; m.p. 126-128°C; IR (KBr pellets): 3329cm⁻¹ (N-H); 1620cm⁻¹ (C=N); 1598cm⁻¹ (C=C); 1023cm⁻¹ (S=O); ¹H-NMR (400



MHz, CDCl₃), δ 6.52-8.12 (m, 14H); δ 5.43 (s, 1H); δ 2.38 (s, 3H); MS(ESI): *m/z* 378 [M⁺]; Anal. Calc. for C₂₁H₁₈FN₃OS: C, 66.67; H, 4.76; N, 11.11; S, 8.46, Found: C, 66.72; H, 4.74; N, 11.07; S, 8.42.

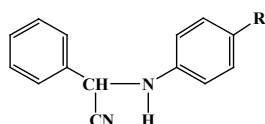
4-Imino-2-[4'-(dimethylamino)phenyl]-5-tolyl-3-phenyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxide (8i): Compound obtained as yellow solid; 72% yield; m.p. 122-124°C; IR (KBr pellets): 3332cm⁻¹ (N-H); 1618cm⁻¹ (C=N); 1590cm⁻¹ (C=C); 1027cm⁻¹ (S=O); ¹H-NMR (400 MHz, CDCl₃), δ 6.52-8.12 (m, 14H); δ 5.43 (s, 1H); δ 2.74 (s, 3H), δ 2.80 (s, 3H); δ 2.38 (s, 3H); MS(ESI): *m/z* 404 [M⁺]; Anal. Calc. for C₂₃H₂₄N₄OS: C, 68.31; H, 5.94; N, 13.86; S, 7.92, Found: C, 68.26; H, 5.91; N, 13.82; S, 7.94.

Results and Discussion

The survey of literature reveals that very few amount of work of *N*-sulphinylanilines have been taken with *N*- α -cyanoamines [16]. The present work aims therefore to study the effect of substituent on aniline part and hence to study their behavior on these cycloaddition reactions and to fill the gap in the literature present study has been taken up in this direction. For the present study, dienophile with cumulative double bond *N*-sulphonyl-4-toluidine has been used for these cycloaddition reactions. *N*-sulphonyl-4-toluidine has been synthesized from pure (AR) grade *p*-toluidine which was further purified by recrystallisation and using doubly distilled thionyl chloride as reported in literature [17]. The *N*-sulphonyl-4-toluidine so obtained was dried over anhydrous sodium sulphate for an overnight period and this was used after distillation in vacuo for these cycloaddition reactions with the *N*- α -cyanoamines.

Various substituted *N*- α -cyanoamines were synthesized by following identical procedure as reported in literature [16]. In the first step, various substituted azomethines were synthesized by condensing substituted anilines with benzaldehyde in alcohol as solvent (Scheme 1) which were subsequently subjected to hydrocyanation using potassium cyanide in aqueous ethanolic solution containing glacial acetic acid and the usual work up yielded crude crystalline *N*- α -cyanoamines (Scheme 2; Table 1).

Then to the solution of *N*- α -cyanoamine in dry toluene a catalytic amount of triethylamine was added followed by the addition of *N*-sulphonyl-4-toluidine 7 (which itself was synthesized using toluidine and thionyl chloride Scheme 3) to provide the desired five-membered heterocyclic compound (Scheme 4) which have been characterized as 4-imino-3-phenyl-2-substitutedphenyl-5-tolyl-2*H*,3*H*,5*H*[1,2,5]



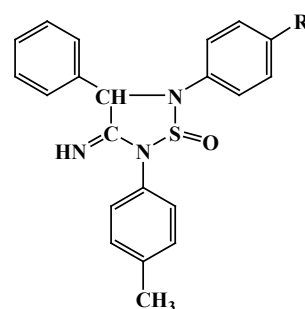
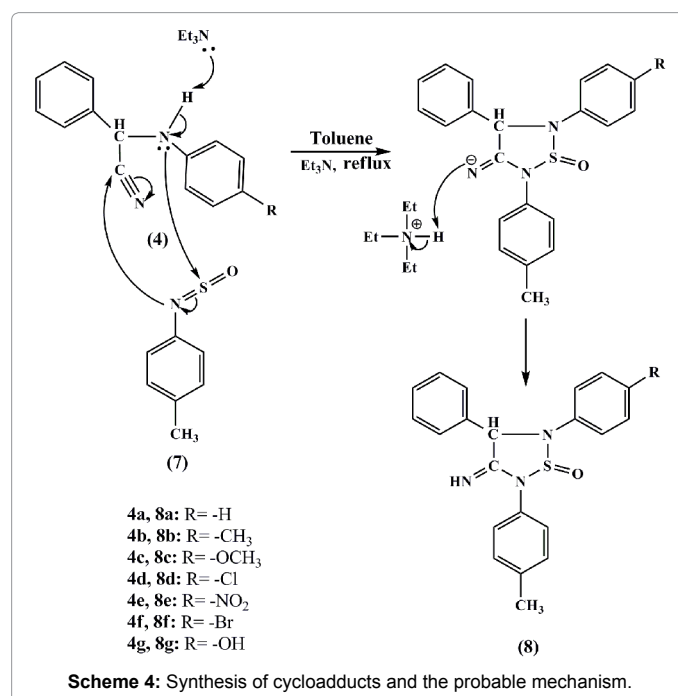
Compounds	R	Melting points in °C	Colour of compounds	% Yield
4a	-H	80-84	White	65
4b	-CH ₃	110-114	White	70
4c	-OCH ₃	44-48	Grey	83
4d	-Cl	78-80	White	58
4e	-NO ₂	140-144	Yellow	81
4f	-Br	90-94	White	68
4g	-OH	108-110	Yellow	69
4h	-F	102-104	White	67
4i	-N(CH ₃) ₂	112-114	Yellow	76

Table 1: Physical characterization data of *N*- α -cyano- α -phenyl methylanilines (4a-i).

thiadiazolidine-1-oxide derivatives as evidenced by thin layer chromatography (TLC) showing the regioselectivity of these 1,3-dipolar cycloadditions.

The reaction afforded only one diastereomer exclusively in all cases, as evidenced by thin layer chromatography (TLC) showing the regioselectivity of these 1,3-dipolar cycloadditions (Table 2).

Structural elucidation of the 4-imino-3-phenyl-2-substitutedphenyl-5-tolyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxides was unambiguously accomplished by using various spectroscopic techniques (IR, ¹H-NMR, ESI-MS) and elemental analyses data as described for compound 8a. The infrared spectrum of 4-imino-2-(4'-tolyl)-5-tolyl-3-phenyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxide 8a exhibited absorption band



Compounds	R	Melting points in °C	%Yield
8a	-H	122-124	64
8b	-CH ₃	116-118	68
8c	-OCH ₃	120-122	62
8d	-Cl	102-104	70
8e	-NO ₂	154-156	65
8f	-Br	114-116	72
8g	-OH	118-120	74
8h	-F	126-128	69
8i	-N(CH ₃) ₂	122-124	72

Table 2: Physical characterization data of 4-Imino-3-phenyl-2-substitutedphenyl-5-tolyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxides (8a-i).

in the region of 3329 cm^{-1} due to N-H_{stretch}, an another band at 1616 cm^{-1} was assigned to C=N_{stretch}, a band at 1590 cm^{-1} was assigned to the skeletal stretching vibrations of the aromatic region and the absorption frequency at 1029 cm^{-1} has been assigned to S=O_{stretch}.

The proton magnetic resonance spectrum of 8a exhibited a multiplet at δ 6.64-8.06 (14H) that was assigned to the aromatic protons (13H) and amino proton (-NH). A singlet at δ 5.31 has been assigned to benzylic proton (1H). While the singlets at δ 2.33 (3H) and δ 2.30 (3H) have been assigned to -CH₃ groups on *N*-phenyl rings of azomethine and *N*-sulphinyl-4-toluidine moieties respectively.

The mass spectrum of 4-imino-2-(4'-tolyl)-5-tolyl-3-phenyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxide revealed the presence of the

molecular ion peak at m/z 375. With loss of *N*-sulphinyl-4-toluidine from the parent ion peak a daughter ion peak at m/z 222 appears which subsequently loses a molecule of hydrocyanic acid to provide another daughter ion peak at m/z 195 *via* 'path a', is present which corresponds to parent azomethine and this cyclises to give ion peak at m/z 194. This mass ion undergoes fragmentation to give mass ion at m/z 107 attributed to *p*-toluidine radical ion which may also arise by the fragmentation and rearrangement of molecular ion. Mass ion at m/z 107 may lose a hydrogen radical to give base peak at mass ion at m/z 106 forming base peak which collapses to mass ion peak at m/z 79 which loses a molecule of ethylene to give mass ion m/z 51. The probable mode of fragmentation is as shown in the Figure 1.

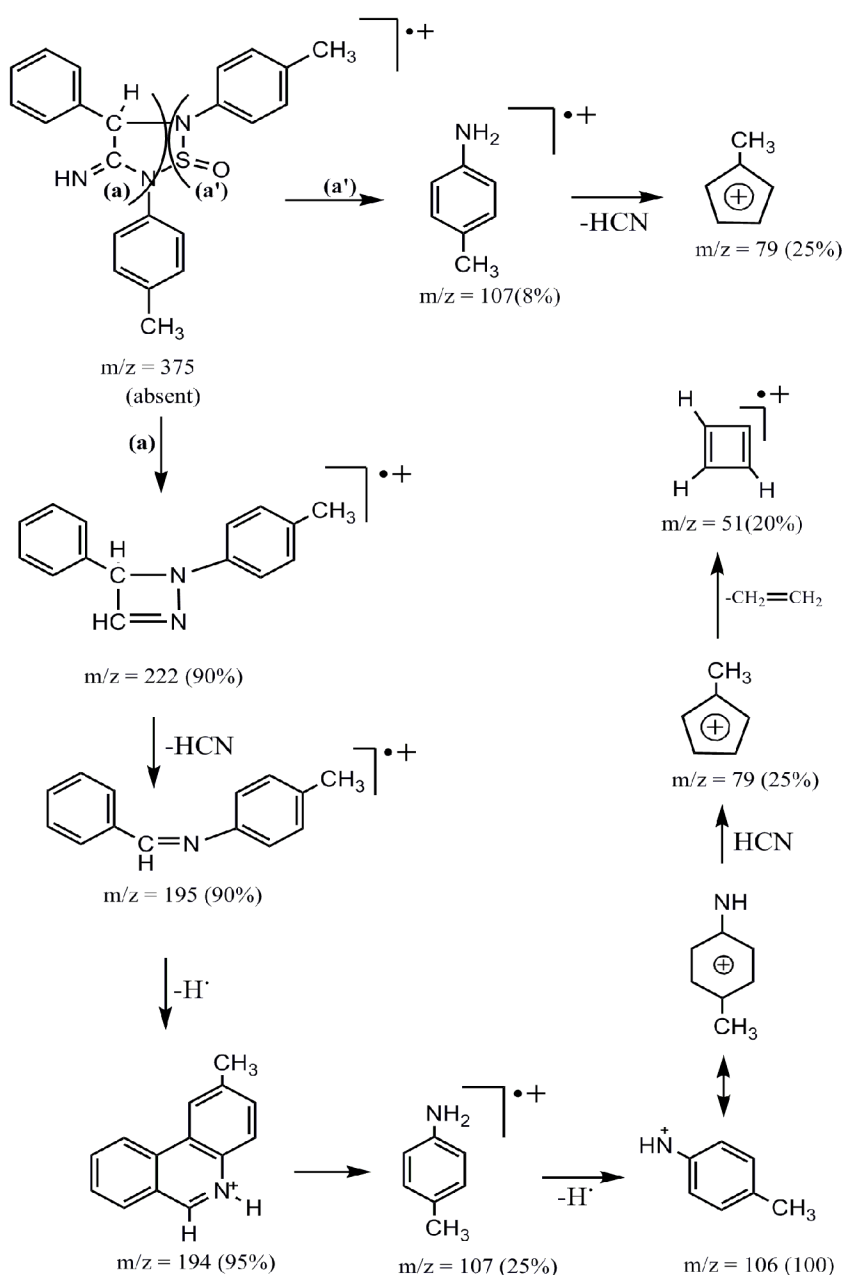


Figure 1: The probable mass fragmentation pattern of 4-Imino-2-(4'-tolyl)-5-tolyl-3-phenyl-2*H*,3*H*,5*H*[1,2,5]thiadiazolidine-1-oxide 8a.

Conclusion

In conclusion, we have successfully developed the regioselective version of bioactive substituted thiadiazolidine derivatives through atom-economic and facile cycloaddition reactions. It was observed that the reaction took place in a stereo- and regioselective pathway across the double bond of the dipolarophiles to give novel thiadiazolidine-1-oxides.

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