An Atom-economic and Facile Synthesis of Novel 4-Imino-3-phenyl-2-substitutedphenyl-5-tolyl-2\textsubscript{H},3\textsubscript{H},5\textsubscript{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, \textsuperscript{1}H-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 RXI FTIR infrared spectrophotometer (manufactured at Buckinghamshire, England) using KBr pellets. \textsuperscript{1}H-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-a-cyano-a-phenyl methylaniline (4a-i)
To substituted benzalaniline (0.02 mol) taken in 250 mL conical
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 was done only after the previous reaction had disappeared in about five hours and the reaction mixture was refluxed for another hour to complete the reaction (Scheme 3). The solvent and excess of thionyl chloride were distilled off under reduced pressure as light yellow solid; 70% yield, m.p. 102-104°C; IR (KBr pellets): 3325 cm-1 (N-H); 1616 (C=N); 1590 cm-1 (C=C); 1030 cm-1 (S=O); 1H-NMR (400 MHz, CDCl3), δ 6.97-8.01 (m, 14H); δ 5.36 (s, 1H); δ 2.32 (3H); MS(ESI): m/z 391 [M]+; Anal. Calc. for C21H19N3O2S: C, 66.84; H, 5.04; N, 11.14; S, 8.42; Found: C, 66.81; H, 5.03; N, 11.12; S, 8.49.

2-(4'-Chlorophenyl)-4-imino-5-tolyl-3-phenyl-2,3-diphenyl-4-imino-5-tolyl-3-phenyl-2-thiadiazolidine-1-oxide (8a):

Scheme 2: Schematic diagram describing the synthesis of substituted N-α-cyanoamines.

Scheme 3: Schematic diagram describing the synthesis of N-sulphonyl-4-toluidine.
Results and Discussion

The survey of literature reveals that very few amount of work of N-sulphonylanilines 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) N-sulphinylaniline which was further purified by recrystallisation 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-2H,3H,5H[1,2,5]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-2H,3H,5H[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-2H,3H,5H[1,2,5]thiadiazolidine-1-oxide 8a exhibited absorption band

MHz, CDCl 3), δ 6.52-8.12 (m, 14H), δ 5.43 (s, 1H), δ 2.74 (s, 3H), δ 2.80 (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.

| Compounds | R | Melting points in °C | Colour of compounds | % Yield |
|-----------|---|---------------------|---------------------|--------|
| 4a        | -H | 80-84               | White               | 65     |
| 4b        | -CH3 | 110-114            | White               | 70     |
| 4c        | -OCH3 | 44-48              | Grey                | 83     |
| 4d        | -Cl | 78-80               | White               | 58     |
| 4e        | -NO2 | 140-144             | Yellow              | 81     |
| 4f        | -Br | 90-94               | White               | 68     |
| 4g        | -OH | 108-110             | Yellow              | 69     |
| 4h        | -F | 102-104             | White               | 67     |
| 4i        | -N(CH3)2 | 112-114        | Yellow              | 76     |

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

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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-2H,3H,5H[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.
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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References

1. Bhat AR, Tazeem, Azam A, Choi I, Athar F (2011) 3-(3,4-Thiadiazole-2-yl) quinoline derivatives: synthesis, characterization and anti-microbial activity. Eur J Med Chem 46: 3158-3166.
2. Foroumadi A, Mansouri S, Emami S, Mirzaei J, Sorkhi M, et al. (2006) Synthesis and antibacterial activity of nitroaryl thiadiazole-tevofloxacin hybrids. Arch Pharm (Weinheim) 339: 621-624.
3. Foroumadi A, Soltani F, Moshafi MH, Ashraf-Askari R (2003) Synthesis and in vitro antibacterial activity of some N-(5-aryl-3,4-thiadiazole-2-yl)piperazinyl quinoline derivatives. Farmaco 58: 1023-1028.
4. Foroumadi A, Emami S, Hassanzadeh A, Rajaei M, Sokhanvar K, et al. (2005) Synthesis and antibacterial activity of N-(5-benzythio-3,4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-3,4-thiadiazol-2-yl)piperazinyl quinoline derivatives. Bioorg Med Chem Lett 15: 4488-4492.
5. Gadad AK, Paikar MB, Anand K, Noolvi MN, Boreddy TS, et al. (2008) Synthesis and biological evaluation of 2-trifluoromethyl/sulfonamido-5,6-diaryl substituted imidazo[2,1-b]-3,4-thiadiazoles: a novel class of cyclooxygenase-2 inhibitors. Bioorg Med Chem 16: 276-283.
6. Gilarini SJ, Khan SA, Siddiqui N (2010) Synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted 2,4-triazolo[3,4-b]-3,4-thiadiazole and 3,4-oxadiazole derivatives of isoniazid. Bioorg Med Chem Lett 20: 4762-4765.
7. Al-Soud YA, Al-Masoudi NA, Loddo R, La Colla P (2008) In-vitro anti-HIV and antitumor activity of new 3,6-disubstituted [2,4]triazolo[3,4-b][3,4]thiadiazoles and thiazidine analogues. Arch Pharm (Weinheim) 341: 365-369.
8. Hamilton PB, Teixeira MM, Stevens JR (2012) The evolution of Trypanosoma cruzi: the ‘bat seeding’ hypothesis. Trends Parasitol 28: 136-141.
9. Chen CJ, Song BA, Yang S, Xu GF, Bhadury PS, et al. (2007) Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonfyl-3,4-thiadiazole and 5-(3,4,5-trimethoxybenzyl)-2-sulfonyl-3,4-oxadiazole derivatives. Bioorg Med Chem 15: 3981-3989.
10. Liu F, Luo XQ, Song BA, Bhadury PS, Yang S, et al. (2008) Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 3,4-thiadiazole and 3,4-oxadiazole moiety. Bioorg Med Chem 16: 3632-3640.
11. Liu XF, Shi YX, Ma Y, Zhang CY, Dong WL, et al. (2009) Synthesis, antifungal activities and 3D-QSPAR study of N-(5-substituted-3,4-thiadiazol-2-yl) cyclopropanecarboxamides. Eur J Med Chem 44: 2782-2786.
12. Hu Y, Li CY, Wang XM, Yang YH, Zhu HL (2014) 3,4-Thiadiazole: synthesis, reactions, and applications in medicinal, agricultural, and materials chemistry. Chem Rev 114: 5572-5610.
13. Wiebe S, Jette N (2012) Pharmacoresistance and the role of surgery in difficult to treat epilepsy. Nat Rev Neurol 8: 669-677.
14. Ulloa CM, Gilliam FG (2011) Epilepsy: Improving care for patients with epilepsy. Nat Rev Neurol 7: 195-196.
15. Siddiqui N, Andalip, Bawa S, Ali R, Afzal O, et al. (2011) Antidepressant potential of nitrogen-containing heterocyclic moieties: An updated review. J Pharm Bioallied Sci 3: 194-212.
16. Singal KK, Singh B, Raj B (1999) Syn Comm 29: 911.
17. Kilmenko LS, Fokin EP (1991) Photolysis of N-nitrosomethylaminooanthraqui- nones. Russ Chem Bull 40: 1858-1862.