

AgOTf-CATALYZED SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NITROGEN/SULFUR-BEARING THIADIAZOLO[3,2-A] PYRIMIDINES

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ABSTRACT

In this study, AgOTf was used as a catalyst to synthesize N, S-thiadiazolo[3,2-a] pyrimidine derivatives, alkyl & aryl Chiral aldoses, and pyrimidine-based amines. A mild reaction procedure involving a Lewis Acid activation of an Aldehyde, followed by a cyclocondensation to produce fused heterocycles in pure analytical form with simple isolation procedures, was employed. Several aryl groups were introduced to install diverse functionalities, and these functionalities were produced in appreciable yields, indicating the robustness of the synthetic procedure and the efficiency of the operation. The designed moiety of the currently prepared derivatives has been analyzed via established methods (M.p, NMR, LC-MS, and other routine analytical methods), and appropriate antimicrobial activity against representative G⁺, G⁻ bacteria and selected fungi has been demonstrated. The fact that multiple derivatives have shown significant activity suggests that the biological response can be tuned by varying substituents on the thiadiazolo[3,2-a] pyrimidine scaffold. This work will contribute to the ongoing search for new antibacterial leads and demonstrate the potential of AgOTf-catalyzed multicomponent reactions to rapidly generate bioactive N/S Compounds, consistent with Sustainable Development Goal 3 in Good Health & Well-Being.

Keywords: Thiadiazolo [3,2 a] Pyrimidines; Nitrogen–Sulfur Heterocycles; AgOTf Catalyst; Multicomponent Synthesis; Antimicrobial Activity

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INTRODUCTION

The heterocyclic moiety containing sulphur and nitrogen atoms is the most powerful emergent form designed in medicinal chemistry and organic chemistry. The countable number of naturally occurring compounds that have these hetero atoms which are used for different biological benefits in several fields. The investigation of structures in drug discovery is a continuous pathway in organic and medicinal chemistry (anti-microbial agents) [Fig.-1].

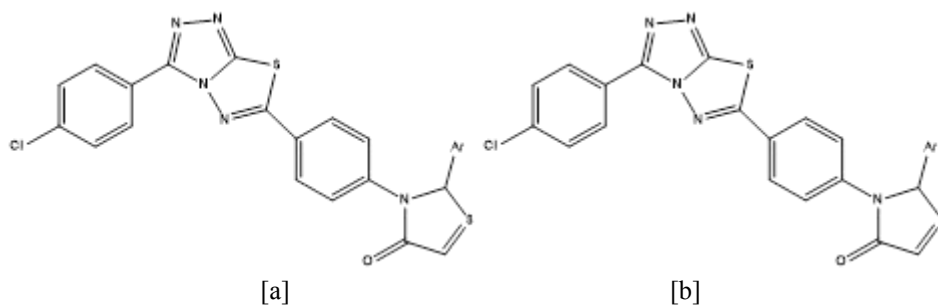


Fig.-1: Anti-Microbial Agents

Nitrogen and sulphur-bearing heterocyclic compounds, having building blocks of great significance to both medical chemistry and organic chemistry, and their synthesis are prolonged to represent a challenge from both academic and industrial perspectives.

The most important hetero cyclic compounds in the azole family that bear a five and six-membered ring in the mother moiety, such as dithiazole and pyrimidine, thiadiazolo [3, 2-a] pyrimidines derivatives. This moiety is fused with Thiadiazols and pyrimidine, which is exhibited by a wide range of emergent significant biological properties. The combination of these two heterocyclic rings with a bridgehead nitrogen atom has attracted interest from several medicinal researchers around the world who want to investigate the established framework for its potential. Additionally, the different properties pertaining to a broad range of pharmacology and biology have been documented.¹⁻⁶ The thiadiazolo [3, 2-a] pyrimidines molecules are a key intermediate in the construction of designed drug moieties and also pharmaceutically potent activity substances. These moieties exhibited a larger number of biological properties, including antimicrobial activity,^{7,8} Anticancer activity,⁹⁻¹² antioxidant activity,¹³⁻¹⁶ antitumor activity,¹⁷ Analgesic,¹⁸ and anti-corrosion activity.¹⁹

The analogues of titled thiadiazolo [3, 2-a] pyrimidines are an important moiety of heterocyclic pharmaceuticals and bioactive natural products because of their potency and wide range of in vitro impacts of the derivatives. The study presented herein provides the rationale and the continuation of research activities directed toward discovering new methodologies for synthesizing N/S-containing heterocycles that exhibit antibiotic activity.

The present work explores the AgOTf-catalyzed multicomponent synthesis of desired derivatives, utilizing starting materials that provide a straightforward route for synthesizing these fused structures. Additionally, the developed compounds were intended to evaluate antimicrobial activity against selected bacterial and fungal strains. This work contributes to the development of new antimicrobial candidates and aligns with Sustainable Development Goal (Good Health and Well-Being) by targeting infectious disease-related challenges.

EXPERIMENTAL

Material and Methods

Meck and Fine Chemicals supplied all synthetic grade chemicals, solvents, and reagents. An Agrawal thermal instrument was to settle or decide the uncorrected melting point of each planned derivative. By using an internal standard as TMS, the NMR spectra of certain derivatives were recorded in CDCl₃ solvent, both proton and carbon NMR spectra, on a Bruker. Thin-layer chromatography with ethyl acetate-n-hexane in various ratios as the eluent and silica gel coated on aluminum plates was used to identify the reaction. LCMS was employed to estimate the molecular weight of each newly synthesized chemical.

General Preparation of (2)

Take 50 mL RBF and 25 mL of acetonitrile, introduce the compound (1) (1mol), which was dissolved in the above solvent. The other reactant, such as thiosemicarbazide (1.125mol), was added to the RBF. The mineral acid, 2.5m conc H₃PO₄, was charged drop-wise into the mixture of solutions, followed by a maintained process of the reactants, which was continued at 600 C for 5 hours. The enhancement of the reaction was identified by TLC and poured into 100 g of crushed ice after completion of the reaction, and also neutralized with a suitable base (NaHCO₃). The final product was washed with polar solvent and washed with water (2 × 50). After the separation of ethyl acetate, distilled off under vacuum, the required compound was finally obtained. M.p-207-209°C. ¹H NMR (400 MHz, CDCl₃) δppm: 1.896 (s, 3H), 2.247 (s, 3H, CH₂), 6.204 (s, 2H), 7.561 - 7.678 (C₆H₆, m, 4H); ¹³CNMR (100 MHz, CDCl₃) δppm: 34.76, 44.09, 128.49, 128.94, 136.66, 140.72, 156.46, and 162.08.

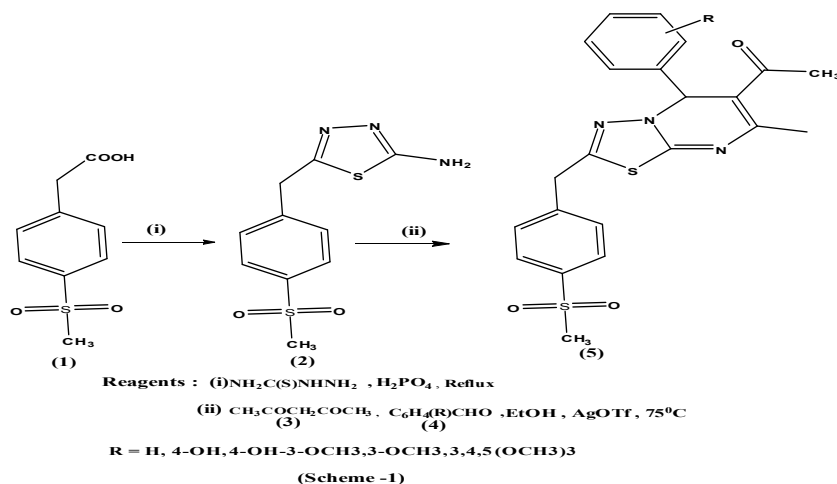
The General Preparation of 1-(7-methyl-2-(4-(methylsulfonyl) benzyl)-5-phenyl-5H-[1,3,4] thiadiazolo [3,2-a] pyrimidin-6-yl) ethan-1-one (5a-5l)

Take a dry and clean 50 mL RB flask and add a mixture of aromatic aldehyde (1.125 moles), compound (3) (1.015 mol), and β-diketone (1.0 mol). Add an appropriate amount of a catalyst, such as palladium acetate, in ethanol to the flask and continue the reaction under reflux for 4-5 hours. It was checked by TLC (5:5, EtOAc: n-hexane) until the consumed raw material. The mixture was then added to crushed ice and neutralized with a dil. HCl aqueous solution. The brine solution was used to wash the desired product layer. The product of the layer was added with Na₂SO₄, and the solid product was obtained after the

solvent was extracted under U/V pressure using a vacuum pump. Each starting material that was produced was recrystallized from pure ethanol alcohol.

RESULTS AND DISCUSSION

The AgOTf-catalyzed two-stage reaction followed smoothly as outlined in the procedure section, providing titled analogous 5a–5l in good to appreciable yields (85–94%). This outcome validates the efficiency of the designed protocol, which leverages the Lewis acidity of AgOTf to activate the aldehyde component and facilitate cyclocondensation with the thiadiazole amine and 1,3-dicarbonyl (Scheme-1). Spectral data (^1H NMR, ^{13}C NMR, LC–MS) for all compounds were fully consistent with the assigned fused heterocyclic structures.



Scheme-1: Synthesis of Fused Pyrimidines 5a–5l

To assess the viability of this approach, the efficiency of four readily available Ag(I) species was evaluated. Notably, AgOTf facilitated nearly complete conversion in a clean reaction within 12 hours, as confirmed by ^1H NMR analysis. In contrast, Triflates of magnesium, zinc, and copper exhibited no reactivity with either aldehyde tested. Among these catalysts, AgOTf demonstrated superior reactivity and a shorter reaction time, resulting in high yield and straightforward handling. The limited performance of the other triflates is consistent with their higher coordination capacities, whereas AgOTf, characterized by lower coordination, enabled more efficient catalysis. Based on these findings and to further investigate the Lewis acid properties of Ag(I), AgOTf was selected as the catalyst, and key reaction parameters were systematically varied to optimize the conditions (Table-1).

Table-1: Catalyst Screening for the Synthesis of Derivative 5f.

S. No	Catalyst	Time (min)	% of Yield
1	$\text{Mg}(\text{OTf})_2$	240	53
2	$\text{Zn}(\text{OTf})_2$	240	69
3	$\text{Cu}(\text{OTf})_2$	240	77
4	AgOTf	240	94

AgOTf proved superior due to its optimal coordination and reactivity under mild conditions, outperforming other triflates of transition metals in both yield and cleanliness of the reaction profile. This catalyst is the most active during the reaction and also preformation of the improvement of the outcome. Hence, it chose the not only the available but also the skimpily handled. The solvent is one of the important parameters during the reaction, and the most significant objective of the synthesis of the designed derivatives of this article.

There are various solvents are applied during the reaction, including CH_3CN , CH_2Cl_2 , $\text{C}_2\text{H}_5\text{OH}$, and $\text{C}_6\text{H}_5\text{CH}_3$, and all the starting materials of this reaction were dissolved by the solubility of the solvent, and also influenced the starting materials in an appropriate time. Among these solvents, Ethanol emerged as

the optimal solvent, offering excellent solubility for the substrates and promoting high conversion without side reactions, as shown below in Table-2.

Table-2: Solvent Screening for the Preparation of Derivative 5f

Entry	Solvent	Time (min)	Yield (%)
1	CH ₃ CN	240	66
2	CH ₂ Cl ₂	240	51
3	C ₂ H ₅ OH	240	94
4	C ₆ H ₅ CH ₃	240	69

The catalyst quantity is a key parameter in this procedure. In its absence, no reaction improvement occurs; an essential amount of catalyst is required. Gradually increasing the catalyst quantity enhanced the yield and reaction rate, achieving up to 92% yield with 30 mmol, as shown in Table-3.

Table-3: Impact of the Amount of Catalyst (5f)

Entry	Catalyst (mmol)	Time (min)	Yield (%)
1	10	210	Traces
2	20	210	48
3	30	210	94
4	40	210	94

A 30 mmol% loading of AgOTf was ideal, providing maximum yield without excess. The ¹H NMR spectra of 5a–5l displayed characteristic aromatic protons (δ 7.8–6.8 ppm), methine proton at C-4 (δ 4.3–4.1 ppm), methyl singlets (δ 2.9–1.2 ppm), and methoxy/OH signals where applicable. ¹³C NMR confirmed the presence of quaternary carbons in the fused ring system (δ 195–150 ppm). Mass spectra showed expected [M+H]⁺ or [M+2]⁺ peaks for halogenated analogues. Electron-donating groups (e.g., methoxy in (5d–5f)) generally afforded higher yields than electron-withdrawing groups (e.g., halogens in (5h–5j)), consistent with enhanced nucleophilicity in the cyclisation step.

Characterization Data of Synthesized Compounds 5a-5l

5a: Yield 86%; m.p. 211–213 °C; ¹H NMR (400 MHz, CDCl₃) δ: 1.308 (s, 3H), 1.846 (s, 3H), 2.230 (s, 3H), 2.662 (s, 2H), 4.268 (s, 1H), 7.273–7.782 (m, 8H, Ph); ¹³C NMR (100 MHz, CDCl₃) δ: 20.88, 28.02, 35.26, 48.07, 64.12, 127.09, 127.71, 128.36, 128.84, 129.45, 130.92, 135.33, 138.02, 141.02, 156.36, 160.21, 163.04, 192.73; LC–MS (m/z): 440.48 [M+H]⁺. Formula: C₂₂H₂₁N₃O₃S₂.

5b: Yield- 88%; m.p. 219–221 °C. ¹H NMR (400 MHz, CDCl₃) δ: 1.550 (s, 3H), 1.864 (s, 3H,), 2.536 (s, 3H), 2.846 (s, 2H, CH₂), 4.304 (s, 1H, C₄), 7.122–7.312 (4H, Ar), 7.515–7.591(2H, Ar), 7.721–7.808 (m, 2H), 9.172 (s, 1H, OH); ¹³C NMR (100 MHz, CDCl₃) δ: 19.82, 27.23, 35.74, 48.02, 62.62, 126.04, 127.38, 128.44, 128.92, 129.02, 131.72, 137.66, 140.25, 150.04, 158.36, 162.02, 190.08; LC–MS (m/z): 456.73 [M+H]⁺. Formula: C₂₂H₂₁N₃O₄S₂.

5d: Product- 90%; ¹H NMR (400 MHz, CDCl₃) δ: 1.311 (s, 3H, CH₃), 1.704 (s, 3H), 2.546 (s, 3H, CH₃), 2.884 (s, 2H, CH₂), 3.716 (s, 3H), 4.104 (s, 1H, C₄), 7.036–7.736 (m, 8H, C₆H₆); ¹³C NMR (100 MHz, CDCl₃) δ: 20.72, 28.46, 35.36, 48.24, 54.34, 63.18, 127.48, 128.08, 129.94, 131.74, 134.48, 137.07, 141.19, 146.66, 155.37, 157.05, 161.17, 190.36 ; LC–MS (m/z): 470.27 [M+H]⁺. Formula: C₂₃H₂₃N₃O₄S₂.

5e: Yield 91%; m.p. 258–260 °C; ¹H NMR (400 MHz, CDCl₃) δ: 1.441 (s, 3H), 1.904 (s, 3H, CH₃), 2.235 (s, 3H), 2.846 (s, 2H, CH₂), 3.694 (s, 3H), 3.784 (s, 3H), 4.113 (s, 1H, C₄), 7.097– 7.710 (m, 8H, Ph); ¹³C NMR (100 MHz, CDCl₃) δ: 20.08, 26.77, 35.46, 48.12, 54.15, 65.05, 125.75, 126.62, 128.59, 129.28, 131.23, 135.36, 137.69, 141.45, 145.18, 146.09, 155.55, 159.06, 161.17, 192.16 ; LCMS (m/z): 498.88 [M+H]⁺. Formula: C₂₃H₂₅N₃O₅S₂.

5f: Yield 94%; m.p. 261–263 °C; ¹H NMR (400 MHz, CDCl₃) δ: 1.504 (s, 3H), 1.817 (s, 3H, CH₃), 2.304 (s, 3H), 2.881 (s, 2H), 3.557 (s, 6H), 3.730 (s, 3H), 4.119 (s, 1H, C₄), 7.148 -7.789(6H, Ar); ¹³C NMR

(100 MHz, CDCl₃) δ : 20.05, 27.11, 34.74, 46.68, 54.09, 58.26, 65.18, 127.38, 128.46, 129.92, 130.29, 131.74, 133.23, 136.64, 140.82, 150.03, 157.74, 160.08, 163.19, 192.08 ; LC-MS (m/z): 530.26 [M+H]⁺. Formula: C₂₅H₂₇N₃O₆S₂.

5g: Yield 88%; m.p. 240–242 °C; ¹H NMR (400 MHz, CDCl₃) δ : 1.449 (3H, s), 1.770 (s, 3H), 1.905 (s, 6H), 2.287 (s, 2H), 2.651 (s, 3H), 4.172 (s, 1H), 6.841–7.158 (4H, C₆H₆), 7.443–7.668 (m, 4H, Ph); ¹³C NMR (100 MHz, CDCl₃) δ : 20.42, 28.09, 38.21, 40.04, 45.06, 66.28, 126.62, 128.15, 128.83, 129.73, 130.33, 132.09, 138.03, 141.44, 145.55, 156.76, 159.02, 162.38, 194.26 ; LC-MS (m/z): 530.26 [M+H]⁺. Formula: C₂₄H₂₆N₄O₃S₂.

5h: Yield 89%; m.p. 249–251 °C ; ¹H NMR (400 MHz, CDCl₃) δ : 1.502 (s, CH₃, 3H), 1.894 (3H, s), 2.132 (s, 3H), 2.473 (s, 3H), 4.266 (s, 1H, C₄), 7.125–7.954 (m, 8H, Ph); ¹³C NMR (100 MHz, CDCl₃) δ : 20.48, 26.66, 37.62, 45.26, 67.28, 127.94, 128.18, 128.64, 129.16, 131.74, 132.62, 136.97, 141.17, 150.17, 157.38, 160.41, 163.15, 197.28; LC-MS (m/z): 459.56 [M+2]⁺. Formula: C₂₂H₂₀FN₃O₃S₂.

5i: Yield 88%; m.p. 257–259 °C; ¹H NMR (400 MHz, CDCl₃) δ : 1.217 (s, 3H, CH₃), 1.602 (s, 3H), 1.881 (s, 3H), 2.476 (s, 2H, CH₂), 4.272 (s, 1H, C₄), 7.152–7.811 (8H, m) ; ¹³C NMR (100 MHz, CDCl₃) δ : 20.39, 28.04, 35.38, 43.17, 66.72, 127.44, 127.81, 128.66, 128.95, 129.46, 130.33, 132.03, 137.64, 141.11, 155.04, 158.24, 161.98, 194.12; LC-MS (m/z): 475.76 [M+2]⁺. Formula: C₂₂H₂₀ClN₃O₃S₂.

5j: Yield 86%; m.p. 254–256 °C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 1.392 (s, 3H, CH₃), 1.804 (s, 3H, CH₃), 2.062 (s, 3H, CH₃), 2.464 (s, 2H, CH₂), 4.203 (s, 1H, C₄), 7.229–7.312 (C₆H₆, 2H), 7.548–7.727 (m, 4H), 7.765–7.784 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ : 19.88, 32.04, 43.19, 66.28, 128.36, 128.88, 129.24, 129.55, 130.19, 131.64, 135.46, 139.02, 157.17, 160.92, 163.24, 195.16; LC-MS (m/z): 519.29 [M+2]⁺. Formula: C₂₂H₂₀BrN₃O₃S₂.

5l: Yield- 86%; m.p. 244–246 °C; ¹H NMR δ : 1.473 (s, 3H, CH₃), 1.960 (s, 3H), 2.440 (s, 3H), 2.962 (s, 3H), 4.316 (s, 1H, C₄), 7.271–7.882 (m, 8H, ph); ¹³C NMR (100 MHz, CDCl₃) δ : 21.15, 28.02, 35.38, 46.61, 65.02, 127.62, 128.36, 128.75, 129.44, 131.07, 133.36, 136.47, 139.36, 141.74, 156.66, 159.03, 162.76, 197.08; LC-MS (m/z): 475.76 [M+2]⁺. Formula: C₂₂H₂₀N₃O₃S₂.

Anti-Microbial Activities

The tested samples were examined for *in vitro* antimicrobial activity by applying the process of micro broth dilution. First, stock solutions of the test derivatives and reference compound were obtained by sequential dilution twice. Next, nutrient media were prepared: Sabouraud dextrose broth for fungi and Mueller-Hinton broth for bacteria.

The inoculum size was then standardized to ensure consistent turbidity among test strains. The *in vitro* evaluation was tested with Gr (+Ve) pathogens, as shown in the table below, and Gr(-Ve) bacterial pathogens, while antifungal activity was assessed against *A. Niger* and *C. albicans*. Reference drugs, including ketoconazole and streptomycin, served as controls for antifungal and antibacterial assays, respectively. Finally, both primary and secondary screenings were conducted to provide supporting evidence for the results. As shown in Table-4, stock solutions (1000 μ g/mL) of the test samples and reference compound were obtained by adding water one after another. The primary recognition 250, 100, and 50 μ g/mL concentrations were used by the analogous after the evaluation of the antibiotic under study was finished. In both this initial assessment and the following screening, the designed analogues were found to be active. Following the secondary assessment, concentrations of 100, 50, and 25 g/mL were noted. The inoculation wells were maintained in a humid environment at 37 °C for the whole night. A minimal inhibitory concentration (MIC) was determined based on the major dilution's inhibition. The preparative compounds demonstrated exceptional inhibition, according to the evaluated samples of the MIC values.

Table-4: *In vitro* Assay Activities (MIC, μ g/mL) of (5a–5l)

Compound	<i>B. subtilis</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>A. nagger</i>	<i>C. albicans</i>
5a	04	08	08	05	05	06
5b	17	12	18	19	15	12

5c	19	17	17	15	10	14
5d	17	17	15	13	17	15
5e	21	20	19	20	19	18
5f	20	21	20	21	18	15
5g	12	14	09	12	13	10
5h	21	22	22	21	07	08
5i	20	19	23	21	08	10
5j	22	20	24	24	18	18
5k	19	17	19	15	19	17
5l	18	20	15	18	18	16
Streptomycin	27	27	27	27	—	—
Ketoconazole	—	—	—	—	22	22
DMSO	—	—	—	—	—	—

Compounds 5a, 5g, 5h, and 5i exhibited excellent antibacterial activity ($\text{MIC} \leq 12 \mu\text{g/mL}$ against most strains), outperforming or matching streptomycin in several cases. Antifungal potency was notable for 5h and 5i ($\text{MIC} 7\text{--}10 \mu\text{g/mL}$ vs. *A. nagger* and *C. albicans*). Derivatives with electron-withdrawing groups (e.g., F, Cl, NO_2 in 5h–5l) showed enhanced antifungal effects, likely due to improved lipophilicity and membrane interaction. These results highlight the thiadiazolo[3,2-*a*] pyrimidine scaffold's potential as an antimicrobial lead and contribute by identifying candidates against resistant pathogens.

CONCLUSION

In conclusion, the present work developed an efficient AgOTf-catalyzed multicomponent method for synthesizing nitrogen- and sulfur-containing derivatives titled compounds from simple starting materials. A protocol feature of titled analogous is operational simplicity, reduced consumption of reaction, a workup process is easy and appreciable outcome, offering an appealing access to these key fused N/S-heterocycles. Antimicrobial assays showed promising activity for several compounds against targeted bacteria and fungi, indicating potential for scaffold optimization into potent agents. This work advances new bioactive heterocycles, aligning with the Sustainable Development Goal.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors made significant contributions to this manuscript, participated in its review, editing and approved the final version for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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