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SYNTHESIS OF (*E*)-5-(3,4-DIMETHOXYBENZYLIDENE)-3-METHYL-6,7-DIHYDROPYRROLO[1,2-*a*]THIENO[3,2-*d*]PYRIMIDIN-9(5*H*)-ONE

Abstract: *A novel compound namely as (E)-5-(3,4-dimethoxybenzylidene)-3-methyl-6,7-dihydropyrrolo[1,2-a]thieno[3,2-d]pyrimidin-9(5H)-one (**AR-99**) was synthesized via two steps starting from ethyl 3-amino-4-methylthiophene-2-carboxylate (**Me-AT-1**). Comprehensive structural characterization using ^{1}H and ^{13}C NMR spectroscopy and HRMS confirms the structural integrity and regioselectivity of the synthesized compounds.*

Keywords: *aromatic aldehyde, cyclisation, methelene condensation, pyrrolidin-2-one, tricyclic thieno[3,2-d]pirimidinone.*

(*E*)-5-(3,4-DIMETOKSIBENZILIDENE)-3-METIL-6,7-DIGIDROPIRROLO[1,2-*a*]TIENO[3,2-*d*]PIRIMIDIN-9(5*H*)-ON SINTEZI

Annotatsiya: *Yangi birikma, ya'ni (E)-5-(3,4-dimetoksibenzilidene)-3-metil-6,7-digidropirrolo[1,2-a]tieno[3,2-d]pirimidin-9(5H)-on (**AR-99**) etil 3-amino-4-metiltiofen-2-karboksilat (**Me-AT-1**) dan boshlab ikki bosqichli sintez orqali olingan. ^{1}H va ^{13}C YaMR spektroskopiyasi hamda YuAMS yordamida to'liq struktura tavsifi olib borildi va sintez qilingan birikmalarning strukturaviy yaxlitligi hamda regioselektivligi tasdiqlandi.*

Kalit so'zlar: *aromatik aldegid, metilen kondensatsiyasi, pirrolidin-2-on, siklizatsiya, trisiklik tieno[3,2-d]pirimidinon.*

СИНТЕЗ (*E*)-5-(3,4-ДИМЕТОКСИБЕНЗИЛИДЕН)-3-МЕТИЛ-6,7-ДИГИДРОПИРРОЛО[1,2-*a*]ТИЕНО[3,2-*d*]ПИРИМИДИН-9(5*H*)-ОНА

Аннотация: *Новый соединение, а именно (E)-5-(3,4-диметоксибензилиден)-3-метил-6,7-дигидропирроло[1,2-a]тиено[3,2-d]пиримидин-9(5H)-он (**AR-99**), было синтезировано в два этапа, начиная с этил-3-амино-4-метилтиофен-2-карбоксилата (**Me-AT-1**). Полная структурная характеристика с использованием спектроскопии ^{1}H и ^{13}C ЯМР, а также ВТМС подтвердила структурную целостность и региоселективность синтезированных соединений.*

Ключевые слова: *ароматический альдегид, метиленовая конденсация, пирролидин-2-он, трициклический тиено[3,2-d]пиримидинон, циклизация.*

INTRODUCTION

Thieno[3,2-d]pyrimidine: Structure, Synthesis, and Applications. Thieno[3,2-*d*]pyrimidine derivatives have garnered significant attention in medicinal and materials chemistry due to their unique fused heterocyclic framework, which imparts notable electronic, pharmacological, and optical properties. This bicyclic system, comprising a thiophene ring fused with a pyrimidine moiety, exhibits structural resemblance to purines, rendering it an attractive scaffold for designing bioactive molecules, including kinase inhibitors, antimicrobial agents, and anticancer therapeutics[1]. The synthetic strategies for thieno[*3,2-d*]pyrimidine involve diverse methodologies, including cyclization of thiophene derivatives with amidines, multicomponent reactions, and transition-metal-catalyzed cross-coupling reactions[2]. Recent advancements have focused on green synthetic approaches, utilizing microwave-assisted synthesis and solvent-free conditions to enhance efficiency and sustainability[3].

The pharmacological relevance of thieno[*3,2-d*]pyrimidine is underscored by its ability to interact with biological targets such as tyrosine kinases, adenosine receptors, and dihydrofolate reductase, making it a promising candidate for anticancer, anti-inflammatory, and antiviral therapies [4]. Furthermore, these derivatives have demonstrated potential in optoelectronic applications due to their electron-rich nature, facilitating the design of organic semiconductors and photovoltaic materials [5].

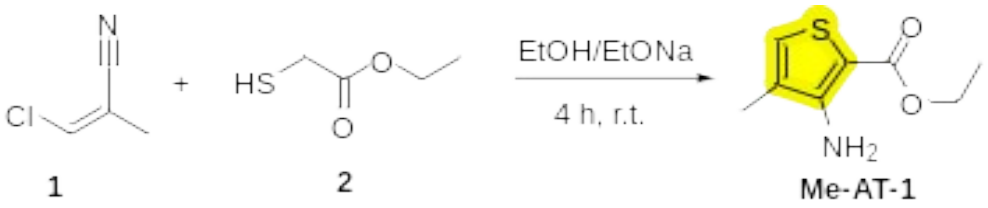
LITERATURE REVIEW

Thieno[*3,2-d*]pyrimidine, a structurally significant fused heterocyclic system, has received considerable attention due to its broad applications in medicinal chemistry, material sciences, and catalysis. This class of compounds, characterized by a thiophene core fused with a pyrimidine ring, shares structural features with purines, making them promising candidates for biologically active molecules. Traditional synthetic routes for thieno[*3,2-d*]pyrimidine derivatives involve condensation reactions between aminothiophenes and cyanamide derivatives or cyclization of thiophene-substituted amidines[6]. However, recent advancements have led to more efficient methodologies, including transition-metal-catalyzed cross-coupling reactions, green chemistry approaches, and microwave-assisted protocols, allowing for improved yields and reduced reaction times[7].

From a pharmaceutical perspective, thieno[*3,2-d*]pyrimidine derivatives have demonstrated potent inhibitory activities against various kinases, including epidermal growth factor receptor (EGFR) and Janus kinase (JAK), making them potential candidates for anticancer therapy. Additionally, their antiviral, anti-inflammatory, and antimicrobial properties have been explored in drug discovery programs aimed at addressing resistant bacterial strains and emerging viral infections[8].

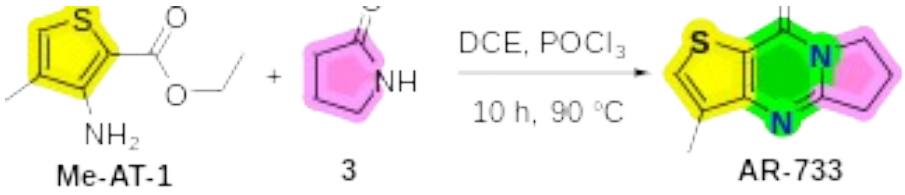
RESEARCH METHODOLOGY

The thienopyrimidine scaffold features multiple reactive centers, making it highly versatile for chemical modifications. Despite its potential, tri- and tetracyclic derivatives of this framework remain relatively underexplored. Our research focuses on expanding the synthetic scope of tricyclic thieno[*3,2-d*]pyrimidines by developing novel derivatives with strategically functionalized cores. In this study, we successfully synthesized a tricyclic thieno[*3,2-d*]pyrimidine system incorporating both aromatic and aliphatic ring moieties. Further structural diversification was achieved through regioselective ether bond formation, enabling precise derivatization and functional fine-tuning.



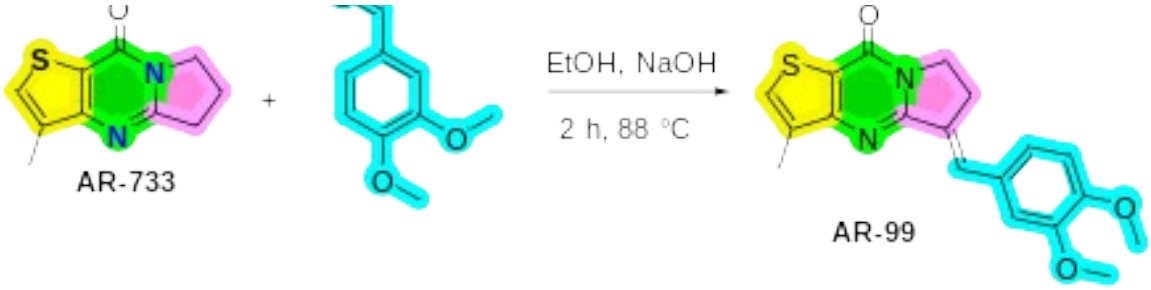
Scheme 1. Reaction reagent and synthesis condition for Me-AT-1.

The synthesis of ethyl 3-amino-4-methylthiophene-2-carboxylate (**Me-AT-1**) commenced with the cyclization of 3-chloroacrylonitrile (**1**) via a nucleophilic substitution mechanism, followed by an intramolecular cyclization. This transformation was facilitated by the reaction with ethyl 2-mercaptoacetate (**2**) under alkaline conditions in ethanol at ambient temperature. The controlled stepwise progression of this reaction enabled the efficient formation of a key thiophene intermediate, essential for subsequent derivatization, as depicted in *Scheme 1*.



Scheme 2. Reaction reagent and condition for forming AR-733.

The subsequent stage of the synthesis entailed a cyclocondensation reaction of **Me-AT-1**, serving as a key precursor. Under acidic conditions, **Me-AT-1** underwent condensation with 2-pyrrolidinone, facilitating the formation of the tricyclic thieno[*3,2-d*]pyrimidine derivative, **AR-733**. This transformation proceeded through an electrophilic cyclization mechanism, promoting annulation and structural rigidity within the fused heterocyclic framework. The optimized reaction conditions ensured regioselective ring closure, yielding **AR-733** with high efficiency and purity (*Scheme 2*).



Scheme 3. Reaction reagent and condition for forming AR-99.

The reactivity of the C ring in the tricyclic thieno[*3,2-d*]pyrimidine system has been systematically investigated. Under alkaline conditions in ethanol, deprotonation occurs due to the high mobility of hydrogen atoms in the methylene group positioned at the α-position. This activation facilitates a condensation reaction between the methylene

group and aromatic aldehydes, ultimately leading to the formation of the arylidene derivative **AR-99**.

ANALYSIS RESULTS

The starting materials were obtained from commercial suppliers and used without further purification. All solvents, including ethanol, petroleum ether, toluene, ethyl acetate, and 1,2-dichloroethane, were anhydrous to avoid moisture interference. Reaction progress was monitored by TLC on $HSGF_{254}$ silica plates (2.5 × 5 cm), with samples applied using 0.3 × 100 mm glass microcapillaries. Chromatograms were visualized under UV light at 254 and 365 nm or by iodine staining. Tetramethylsilane (TMS) was used as an internal standard in NMR analysis. Structural characterization was carried out using ^{1}H and ^{13}C NMR spectra recorded on a VARIAN 400 MHz spectrometer at room temperature. HRMS was performed on a QTRAP® 6500+ LC-MS system to confirm molecular composition and structure.

*Preparation of ethyl 3-amino-4-methylthiophene-2-carboxylate (**Me-AT-1**).*

A 250 mL round-bottom flask was charged with 50 mL of ethanol and 11 mL of ethyl 2-mercaptoacetate (100 mmol, 12 g, ρ = 1.090 g/mL), followed by mixing and cooling to 0 °C under stirring with a reflux condenser. Sodium ethanolate (14.4 g, 210 mmol) was added gradually to control the exothermic reaction. A solution of 3-chloro-2-methylacrylonitrile (8 mL, 100 mmol, 8.75 g, ρ = 1.096 g/mL) in 20 mL ethanol was added dropwise via a dropping funnel. The mixture was stirred at ambient temperature for 4 h. Reaction progress was monitored by TLC (petroleum ether/ethyl acetate 3:1, Rf = 0.77). After column chromatography, ethyl 3-amino-4-methylthiophene-2-carboxylate (AT-1) was obtained as a white solid (14.8 g, 80% yield). The melting point of the compound was found to be 80-81 °C[9].

*Preparation of 3-methyl-6,7-dihydropyrrolo[1,2-a]thieno[3,2-d]pyrimidin-9(5H)-one (**AR-733**).*

A high-pressure 15 mL reaction vessel was loaded with 3 mL of anhydrous dichloroethane (DCE), followed by the gradual dissolution of Me-AT-1 (185 mg, 1 mmol) under continuous stirring. Subsequently, pyrrolidin-2-one (102 mg, 1.2 mmol) was introduced into the reaction medium. To facilitate the transformation, phosphoryl trichloride ($POCl_3$, 0.1 mL) was carefully added dropwise over a period of 20 minutes under controlled conditions to regulate the reactivity. The reaction system was then

heated to 90 °C in a glycerol bath and maintained at this temperature overnight, with reaction progression monitored via thin-layer chromatography (TLC). After completion, purification was performed through column chromatography employing a petroleum ether/ethyl acetate (1:1) solvent system, yielding the target compound, 3-methyl-6,7-dihydropyrrolo[*1,2-a*]thieno[3,2-*d*]pyrimidin-9(5*H*)-one (**AR-733**). The isolated product, obtained as a light white solid (182.5 mg), demonstrated an Rf value of 0.50 and a melting point of 180–181 °C, with a yield of 88.48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 1.2 Hz, 1H), 4.23 (t, *J* = 7.3 Hz 2H), 3.21 (t, *J* = 7.9 Hz, 2H), 2.39 (d, *J* = 1.1 Hz, 3H), 2.37 – 2.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.82, 159.73, 143.60, 131.30, 127.05, 121.25, 46.59, 29.82, 19.53, 14.39. HRMS (ESI) calcd for $C_{10}H_{10}N_2OS$ [M+H]+ 207.0587 found 207.0586.

*Preparation of 5-(3,4-dimethoxybenzylidene)-3-methyl-6,7-dihydropyrrolo[1,2-a]thieno[3,2-d]pyrimidin-9(5H)-one (**AR-99**)*

A 50 mL flask was loaded with 3 mL of anhydrous ethanol. Subsequently, 40 mg of NaOH and 103 mg of AR-733 were added and stirred using a magnetic stirrer. Finally, 116.3 mg of 3,4-dimethoxybenzaldehyde was introduced, and the reaction mixture was heated to 88 °C under reflux with continuous stirring. The reaction progress was monitored via TLC, confirming completion within 2 hours. Purification by column chromatography afforded 114 mg of a white solid identified as 5-(3,4-dimethoxybenzylidene)-3-methyl-3*a*,6,7,9*a*-tetrahydropyrrolo[*1,2-a*]thieno[*3,2-d*]pyrimidin-9(*5H*)-one (**AR-99**) with a 64% yield. The compound exhibited an Rf value of 0.35 in a petroleum ether/ethyl acetate (1:1) solvent system and a melting point of 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, *J* = 2.8 Hz, 1H), 7.41 (q, *J* = 1.1 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 4.31 (dd, *J* = 8.0, 6.6 Hz, 2H), 3.95 (d, *J* = 3.1 Hz, 6H), 3.37 – 3.28 (m, 2H), 2.46 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.90, 157.67, 157.55, 149.80, 149.00, 133.95, 129.94, 129.20, 129.07, 128.67, 123.03, 121.13, 112.79, 111.23, 55.97, 55.95, 43.94, 25.94, 13.01. HRMS (ESI) calcd for $C_{19}H_{18}N_2O_3S$ [M+H]+ 355.1111, found 355.1106.

CONCLUSION

This study established an efficient synthetic route to novel tricyclic thieno[3,2-d]pyrimidine derivatives, allowing the preparation of structurally diverse analogs in high yields and purity. The synthesis involved stepwise core construction and key

transformations, including cyclocondensation to AR-733 and its conversion to AR-99. Structural characterization by ^{1}H and ^{13}C NMR and HRMS confirmed the identity of the compounds. Incorporation of both aromatic and aliphatic substituents expanded the chemical diversity. These results provide a solid foundation for further pharmacological evaluation of these compounds as potential bioactive agents.

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