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A Green and Efficient Monosodium Glutamate-Catalyzed Aqueous Synthesis of 4-Aryl-2-Aminothiazole Derivatives

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Abstract:,*A simple, green, and efficient method has been developed for the synthesis of 4-aryl-2-aminothiazole derivatives using monosodium glutamate (MSG) as a mild organocatalyst in aqueous medium. The reaction involves the condensation of substituted phenacyl bromides with thiourea in water at 80–90 °C and proceeds smoothly within short reaction times. The method avoids the use of hazardous acids and organic solvents, making it environmentally friendly. A variety of aryl-substituted 2-aminothiazoles were obtained in good to excellent yields with simple work-up procedures. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectral analyses. This protocol offers a sustainable alternative to conventional methods and demonstrates the potential of amino acid-based catalysts in heterocyclic synthesis.*

Keywords:4-Aryl-2-aminothiazoles; Monosodium glutamate; Green synthesis; Aqueous medium; Organocatalysis; Heterocyclic compounds

I. INTRODUCTION

The 2-aminothiazole scaffold is a heterocyclic nucleus in medicinal chemistry and is widely encountered in biologically active compounds exhibiting anticancer, antimicrobial, anti-inflammatory, antiviral, and enzyme inhibitory activities (Jain, S.et al 2018;Kumar, A. et al 2016; Mishra, R. et al 2017). Owing to these diverse pharmacological properties, 2-aminothiazole derivatives have attracted sustained attention from synthetic and medicinal chemists. Among these, 4-aryl-2-aminothiazoles are of particular interest due to their presence in several pharmaceutical lead compounds, agrochemicals, and functional materials (Andrade, C. K. Z. et al 2020; Singh, S.et al 2019).Traditionally, the synthesis of 2-aminothiazoles is accomplished through the Hantzsch thiazole synthesis, which involves the condensation of α-halocarbonyl compounds (such phenacyl bromides) with thiourea or thioamides under acidic or oxidative conditions (Hantzsch, A.1887; Gewald, K.1996). Although this method remains widely employed, it often requires strong acids, prolonged reaction times, or hazardous reagents.Acid catalysis plays a crucial role in heterocyclic ring construction by activating electrophilic carbonyl moieties, facilitating nucleophilic attack, and promoting intramolecular cyclization (Joule, J. A.et al 2010). Conventional acidic systems employed in 2-aminothiazole synthesis include Brønsted acids, Lewis acids, and halogenating agents, which generate reactive electrophilic intermediates in situ (Yadav, G.D.et al 2004; Zolfigol, M. A. et al 2015) . However, many of these protocols suffer from disadvantages such as harsh reaction conditions, environmental toxicity, limited functional-group tolerance, and poor sustainability, prompting the search for greener alternatives (Anastas, P. T. et al 1998).Monosodium glutamate (MSG), the sodium salt of the naturally occurring amino acid glutamic acid, is extensively used as a food additive and is recognized for its low toxicity, biodegradability, and environmental safety (Walker, R.et al 2010). Structurally, MSG contains carboxylate and amino functional groups, which may enable mild Brønsted acid–base behavior and hydrogen-bonding interactions, suggesting its potential application as a benign organocatalyst under suitable reaction conditions (Carey, F. A. et al 2007).

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The concept of employing small organic molecules as catalysts is well established within the field of organocatalysis, where simple, metal-free compounds accelerate chemical reactions via acid–base activation, hydrogen bonding, or iminium/enamine intermediates (List, B.2007; MacMillan, D. W. C. 2008). In recent years, amino acid-based catalysts and their salts have emerged as attractive alternatives to conventional catalysts due to their low cost, availability, and eco-friendly nature (Mukherjee, S. et al 2007).Despite its widespread use in food chemistry and emerging applications in green synthesis, reports on MSG functioning as an acid catalyst in heterocyclic ring formation are scarce. Nevertheless, MSG has been successfully employed as a catalyst in multicomponent organic reactions, including aqueous-phase syntheses under microwave irradiation, such as the preparation of isoxazolone derivatives, demonstrating its ability to promote bond formation under mild and environmentally benign conditions (Jadhav, S. D. et al 2016; Patil, R. S. et al 2019).In this research work, a systematic investigation into the MSG-catalysed synthesis of 4-aryl-2-aminothiazoles represents a promising and sustainable alternative to conventional methods. The use of MSG as a mild acid catalyst may facilitate the activation of electrophilic α-halocarbonyl compounds, enabling nucleophilic addition of thiourea followed by cyclization to afford the desired thiazole derivatives under green reaction conditions. Such an approach aligns with the principles of sustainable and green chemistry and may expand the scope of amino acid-based organocatalysts in heterocyclic synthesis (Sheldon, R. A.2012).

II. EXPERIMENTAL

2.1 Materials and Methods

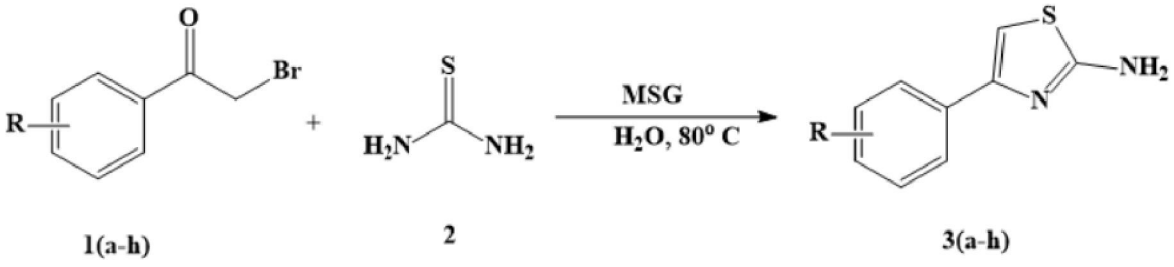
All reagents and solvents were of analytical grade and used without further purification. Aromatic phenacyl bromides,thiourea and monosodium glutamate (MSG) were obtained from standard suppliers. Reactions were carried out in distilled water. Reaction progress was monitored by thin-layer chromatography (TLC) using silica gel plates.

General Procedure for the Synthesis of 4-Aryl-2-Aminothiazole Derivatives

A mixture of substituted phenacyl bromide (1.0 mmol), thiourea (1.0 mmol), and monosodium glutamate (10 mol%) was taken in a round-bottom flask containing 10 mL of distilled water. The reaction mixture was stirred at 80–90 °C for 30–60 min.

The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 6:4). After completion, the reaction mixture was allowed to cool to room temperature. The solid product formed was filtered, washed with cold water to remove residual catalyst, and recrystallized from ethanol to afford pure 4-aryl-2-aminothiazole derivatives. The synthesized compounds were confirmed by taking their melting points and by using ^{1}H NMR, ^{13}C NMR and IR spectroscopic techniques.

2.2 General Reaction



Scheme: Reaction of Phenacyl bromide and thiourea using Monosodium Glutamate as a catalyst

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2.3 Reaction Outcome and Yield

Entry	Substituent (R)	Time (min)	Yield (%)	M.P (°C)
a	-H	45	82	134-135
b	4-Chloro	40	88	169-170
c	4-Nitro	30	90	280-282
d	4-Methoxy	50	78	208-210
e	4-Methyl	45	80	134-136
f	4-Fluoro	40	80	121-122
g	3-Nitro	35	85	182-183
h	4-Hydroxy	30	85	133-134

The results demonstrate that MSG is an effective catalyst, providing high yields in short reaction times without the need for hazardous acids or organic solvents.

2.4 Results and Discussion

The present methodology demonstrates an efficient MSG-catalyzed synthesis of 4-aryl-2-aminothiazoles in aqueous medium. The reactions proceeded smoothly under mild conditions, affording moderate to excellent yields.

MSG acts as a mild Brønsted acid catalyst, activating the carbonyl group of the phenacyl bromide and facilitating nucleophilic attack by thiourea. Subsequent cyclization and elimination steps lead to the formation of the thiazole ring. The zwitterionic nature of MSG assists proton transfer and stabilizes reaction intermediates via hydrogen bonding.

Electron-withdrawing substituents on the aromatic ring generally enhanced reaction rates and yields, while electron-donating groups required slightly longer reaction times. Notably, the aqueous medium improved operational simplicity and minimized environmental impact.

2.5 Spectral Analysis

2.5.1 Synthesis of 4-Phenyl-2-aminothiazole (3a)

White solid, IR(KBr): 3370 cm^{-1}, 3050 cm^{-1}, 1595 cm^{-1}, 1475 cm^{-1}, 1315 cm^{-1}, 740 cm^{-1};
^{1}H NMR: δ 5.30–5.80 (s, 2H), δ 7.20–7.40 (m, 3H),δ 7.45–7.60 (m, 2H),δ 7.65–7.85 (s, 1H);
^{13}C NMR (100 MHz, DMSO-d□, δ ppm): δ 168–170, δ 148–150, δ 134–136,δ 128–130, δ 125–127, δ 115–118

2.5.2 Synthesis of 4-(4-Nitrophenyl)-2-aminothiazole (3c)

Yellow solid, IR(KBr): 3340 cm^{-1}, 3050 cm^{-1}, 1620cm^{-1} ,1505 cm^{-1},1335 cm^{-1},1480 cm^{-1} 750 cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d□, δ ppm)δ 5.60–6.10 (s, 2H) δ 7.55–7.70 (d, J ≈ 8.5 Hz, 2H) δ 8.10–8.25 (d, J ≈ 8.5 Hz, 2H) δ 7.80–7.95 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d□, δ ppm) δ 168–170 δ 150–152 δ 146–148 δ 138–140 δ 127–130 δ 124–126 δ 115–118

2.5.2 Synthesis of 4-(4-Fluorophenyl)-2-aminothiazole

Pale yellow solid, IR (KBr): 3405 cm^{-1}, 3050 cm^{-1}, 1610 cm^{-1}, 1515 cm^{-1}, 1230cm^{-1} , 750 cm^{-1} ;^{1}H NMR (400 MHz, DMSO-d□): δ 5.30–5.80 (s, 2H) : –NH□ protons δ 7.05–7.20 (t, J ≈ 8.5 Hz, 2H), δ 7.40–7.55 (t, J ≈ 8.5 Hz, 2H), δ 7.60–7.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d□): δ 168–170 , 150–152, δ 162–164 (d, JCF ≈ 240 Hz), δ 128–130, δ 115–118 (d, JCF ≈ 20 Hz) , δ 116–118

III. CONCLUSION

An efficient, environmentally benign, and sustainable protocol for the synthesis of 4-aryl-2-aminothiazole derivatives has been developed using monosodium glutamate as a green organocatalyst in water. The method offers several advantages, including mild reaction conditions, simple work-up, good to excellent yields, and avoidance of toxic reagents. This approach highlights the potential of amino acid-based catalysts in heterocyclic synthesis and aligns well

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withthe principles of green chemistry. The methodology is expected to find applications in medicinal and synthetic organic chemistry.

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