IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736. Volume 19, Issue 8 Ser. I (August. 2026), PP 01-05
www.iosrjournals.org

Sulphanilic Acid: An Effective Catalyst For The One-Pot Synthesis Of [1,2,4] Triazoloquinazolinone Derivatives

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Abstract
A highly efficient, eco-friendly, and simple one-pot three-component synthesis of fused [1,2,4] triazoloquinazolinone derivatives has been developed utilizing sulphanilic acid (4-aminobenzenesulfonic acid) as an inexpensive, non-toxic, and readily available solid acid catalyst. The reaction involves the multicomponent condensation of 3-amino-1,2,4-triazole, substituted aromatic aldehydes, and dimedone (or 1,3-cyclohexanedione) under ethanol reflux conditions. Optimized reaction parameters (10 mol% sulphanilic acid in EtOH at 78°C) afforded the target heterocycles in high to excellent yields (88-96%) within significantly shortened reaction times (25-45 min). The catalyst exhibited good operational stability and could be recovered and reused for up to four consecutive cycles without appreciable loss of catalytic efficiency. All synthesized compounds were characterized by 1H NMR, 13C NMR, FTIR, and high-resolution mass spectrometry (HRMS).

Keywords: *Sulphanilic acid, Multicomponent reaction, One-pot synthesis, [1,2,4] Triazoloquinazolinones, Green chemistry, Solid acid catalyst.*

Date of Submission: 24-07-2026 Date of Acceptance: 04-08-2026

I. Introduction

Multicomponent reactions (MCRs) have emerged as an indispensable cornerstone in modern synthetic organic chemistry, medicinal chemistry, and drug discovery pipeline development [1-4]. MCRs facilitate the rapid construction of complex molecular architectures with remarkable atom-economy, high step-efficiency, minimal solvent consumption, and simplified isolation procedures compared to traditional step-by-step synthetic sequences [5-7]. The ability to assemble three or more readily accessible starting materials into a single core structure in a single operational step inherently adheres to the core tenets of Green Chemistry [8-10].

Nitrogen-containing fused heterocycles represent a privileged class of structures in pharmacologically active natural products and synthetic drugs [11-13]. Among these, quinazolinone fused derivatives specifically [1,2,4] triazolo quinazolinones occupy a high-priority position owing to their broad range of biological activities [14,15]. Triazoloquinazolinones exhibit substantial therapeutic potential, functioning as antimicrobial [16], antifungal [17], anti-inflammatory [18], analgesic [19], anticancer [20], antihypertensive [21], and anticonvulsant agents [22]. Furthermore, they are recognized as selective kinase inhibitors [23] and potent adenosine receptor antagonists in neurodegenerative disorder models [24]. Consequently, numerous synthetic methodologies have been documented for the preparation of [1,2,4] triazolo quinazolinone scaffold variants [25-27]. Classical protocols typically employ multi-step condensation reactions requiring harsh mineral acids (e.g., concentrated H_2SO_4, HCl), toxic Lewis acid catalysts (e.g., $AlCl_3$, $SnCl_4$), high boiling hazardous organic solvents, extended reaction times, and laborious chromatographic purification steps [28, 29]. Recently, improved methodologies utilizing homogeneous and heterogeneous catalysts such as p-TSA, ionic liquids, silica-supported sulfuric acid, nano-catalysts, and metal triflates have been reported [30, 31]. However, many of these existing catalyst systems suffer from notable drawbacks, including high catalyst cost, complex catalyst preparation procedures, moisture sensitivity, toxicity, and poor reusability [32, 33].

In this context, the development of inexpensive, eco-safe, environmentally benign, and operational catalytic systems remains highly desirable [34, 35]. Sulphanilic acid (4-aminobenzenesulfonic acid) is a commercially available, non-toxic, inexpensive, zwitterionic solid acid bearing both a strongly acidic sulfonic acid ($-SO_3H$) group and an amino ($-NH_2$) functionality. Due to its solid state nature, low volatility, and moderate acidity, sulphanilic acid serves as an efficient organocatalyst in various organic transformations such as synthesis of xanthenes, bis(indolyl)methanes, and quinoxalines. However, its potential application in the multicomponent synthesis of triazoloquinazolinones has not been fully explored.

Herein, we present a straightforward, highly efficient, and green protocol for the one-pot three-component synthesis of substituted [1,2,4]triazoloquinazolinone derivatives via condensation of 3-amino-1,2,4-

triazole, aromatic aldehydes, and dimedone (or 1,3-cyclohexanedione) catalyzed by catalytic amounts of sulphanilic acid in ethanol under reflux conditions.

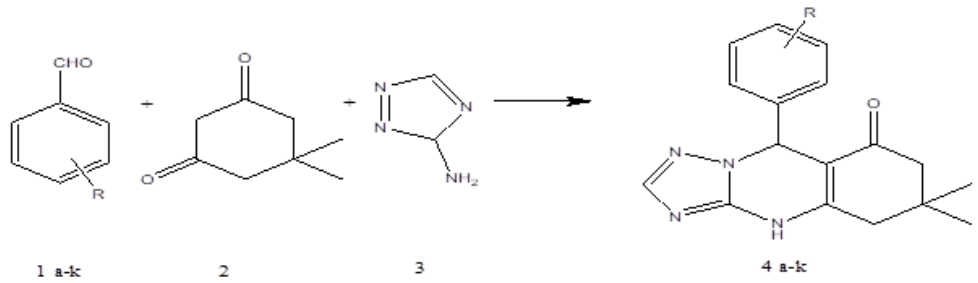
II. Experimental Section

General Information

All chemicals, reagents, and solvents were purchased from commercial chemical suppliers (Sigma-Aldrich, Alfa Aesar, Merck) and used without further purification. Melting points were measured in open capillary tubes using a digital Buchi B-540 melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance III spectrometer using DMSO-d6 as the solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm). FTIR spectra were recorded on a PerkinElmer Spectrum Two spectrophotometer using KBr pellets in the range of 4000-400 cm^{-1}. High-resolution mass spectra (HRMS) were obtained on an Agilent 6540 Q-TOF mass spectrometer.

General Synthetic Procedure for [1,2,4] Triazoloquinazolinones (4a-j)

A mixture of 3-amino-1,2,4-triazole (1.0 mmol), substituted aromatic aldehyde (1.0 mmol), dimedone or 1,3-cyclohexanedione (1.0 mmol), and sulphanilic acid (10 mol%, 0.10 mmol, 17.3 mg) in absolute ethanol (5.0 mL) was stirred under reflux conditions for the appropriate duration (20-45 min, monitored by TLC using ethyl acetate:n-hexane 4:6 as eluent). Upon completion of the reaction, the reaction mixture was allowed to cool to room temperature. The precipitated solid product was collected by filtration, washed with cold ethanol (2 × 5 mL) and warm water to remove residual catalyst. The crude solid product was recrystallized from hot ethanol to afford analytically pure [1,2,4]triazoloquinazolinone derivatives in high yields.



Scheme: Synthesis of 1,2,4-triazolo[5,1-b] quinolin-8(4H)-one derivatives

III. Results And Discussion

To establish the optimum reaction conditions, a model three-component reaction was examined utilizing 3-amino-1,2,4-triazole (1.0 mmol), 4-chlorobenzaldehyde (1.0 mmol), and dimedone (1.0 mmol) as test substrates. The reaction parameters including catalyst loading, choice of solvent, and reaction temperature were systematically investigated, as detailed in Table 1.

Entry	Catalyst (mol%)	Solvent	Temp (°C) / Condition	Yield (%)a
1	None	Ethanol	Reflux (78 °C)	18
2	Sulphanilic Acid (2.5)	Ethanol	Reflux (78 °C)	54
3	Sulphanilic Acid (5.0)	Ethanol	Reflux (78 °C)	78
4	Sulphanilic Acid (10.0)	Ethanol	Reflux (78 °C)	95
5	Sulphanilic Acid (15.0)	Ethanol	Reflux (78 °C)	94
6	Sulphanilic Acid (10.0)	Water	Reflux (100 °C)	62
7	Sulphanilic Acid (10.0)	Methanol	Reflux (65 °C)	86
8	Sulphanilic Acid (10.0)	Acetonitrile	Reflux (82 °C)	71
9	Sulphanilic Acid (10.0)	Solvent-free	100 °C	80
10	p-TSA (10.0)	Ethanol	Reflux (78 °C)	89

Table 1: Optimization of reaction parameters for the model reaction. aIsolated yields after crystallization.

As clearly demonstrated in Table 1, performing the reaction in the absence of catalyst produced only a trace yield (18%) of the target product after 3 h of reflux in ethanol (Entry 1). Introduction of sulphanilic acid markedly accelerated the reaction rate and improved target product yield. Incrementing catalyst loading from 2.5 mol% to 10 mol% enhanced the isolated yield from 54% to 95% (Entries 2-4). Increasing catalyst loading beyond 10 mol% (e.g., 15 mol%, Entry 5) produced no measurable gain in yield or rate. Solvent evaluation revealed ethanol as the superior solvent relative to methanol, water, and acetonitrile (Entries 6-8). A solvent-free approach at 100 °C yielded 80% product but gave slight impurities (Entry 9). Consequently, 10 mol% sulphanilic acid in ethanol under reflux was identified as the standard optimized system.

Substrate Scope and Generality

With optimal parameters established, the generality and substrate scope of this catalytic protocol were explored using a diverse series of substituted aromatic aldehydes and 1,3-dicarbonyl compounds (dimedone and 1,3-cyclohexanedione). The results are summarized in Table 2.

Product	Ar Group	Dione (R)	Time (min)	Yield (%)a	mp (°C) [Lit.]
4a	C_6H_5	Dimedone (Me)	30	92	234-236
4b	4-Cl-C_6H_4	Dimedone (Me)	25	95	248-250
4c	4-NO_2-C_6H_4	Dimedone (Me)	20	96	262-264
4d	4-OMe-C_6H_4	Dimedone (Me)	40	89	210-212
4e	4-Me-C_6H_4	Dimedone (Me)	35	90	222-224
4f	2-Cl-C_6H_4	Dimedone (Me)	30	93	240-242
4g	3-NO_2-C_6H_4	Dimedone (Me)	25	94	255-257
4h	4-Br-C_6H_4	Dimedone (Me)	25	95	258-260
4i	4-Cl-C_6H_4	1,3-Cyclohexanedione (H)	30	91	242-244
4j	4-OMe-C_6H_4	1,3-Cyclohexanedione (H)	45	88	204-206

Table 2: Substrate scope for sulphanilic acid-catalyzed synthesis of [1,2,4]triazoloquinazolinones 4a–j. aIsolated yields.

As demonstrated in Table 2, both electron-withdrawing groups (-Cl, -Br, -NO_2) and electron-donating groups (-OMe, -Me) on the aromatic aldehyde ring were well-tolerated. Aldehydes bearing electron-withdrawing substituents reacted slightly faster and gave higher yields (93-96%) due to heightened electrophilicity of the carbonyl center. Conversely, electron-donating groups required marginally extended reaction times (35-45 min) while maintaining excellent isolated yields (88-90%). Substitution at ortho, meta, and para positions proceeded smoothly without adverse steric inhibition.

Catalyst Recyclability

The reusability of sulphanilic acid was evaluated in the model reaction (formation of 4b). Upon reaction completion, ethanol was partially concentrated, and hot water was added. Sulphanilic acid dissolves readily in hot water while the product precipitates out. Alternatively, taking advantage of its limited solubility in cold ethanol/ether, the catalyst was filtered, washed with cold ethanol, dried in an oven at 80 °C for 2 h, and directly reused in subsequent reaction runs. As depicted in Figure 1, the catalytic efficiency remained largely intact through 4 consecutive cycles (Run 1: 95%, Run 2: 94%, Run 3: 92%, Run 4: 90%).

Spectral Characterization Data for Representative Products

9,9-Dimethyl-6-phenyl-6,7,8,9-tetrahydro-[1,2,4] triazolo[5,1-b] quinazolin-8(5H)-one (4a): White solid; Yield 92%; mp 234-236 °C; FTIR (KBr, cm^{-1}): 3280 (NH), 3060 (Ar-H), 2955 (C-H aliphatic), 1665 (C=O), 1610 (C=N), 1545, 1380, 1245. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 0.98 (s, 3H, CH3), 1.08 (s, 3H, CH3), 2.12 (d, J = 16.0 Hz, 1H, CH2), 2.30 (d, J = 16.0 Hz, 1H, CH2), 2.61 (s, 2H, CH2), 6.32 (s, 1H, CH-chiral), 7.15-7.32 (m, 5H, Ar-H), 7.82 (s, 1H, triazole-H), 10.85 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 27.2, 28.9, 32.4, 50.3, 58.4, 108.2, 126.8, 127.5, 128.6, 141.2, 150.1, 152.4, 162.8, 193.5. HRMS (ESI-TOF) m/z: $[M+ H]^+$ Calcd for $C_{17}H_{18}N_5O$ 292.1506; Found 292.1512.

6-(4-Chlorophenyl)-9,9-dimethyl-6,7,8,9-tetrahydro-[1,2,4] triazolo[5,1-b] quinazolin-8(5H)-one (4b): Off-white solid; Yield 95%; mp 248-250 °C; FTIR (KBr, cm^{-1}): 3275 (NH), 3055, 2960, 1668 (C=O), 1612 (C=N), 1540, 1090 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 0.97 (s, 3H, CH3), 1.06 (s, 3H, CH3), 2.10 (d, J = 16.2 Hz, 1H, CH2), 2.28 (d, J = 16.2 Hz, 1H, CH2), 2.60 (s, 2H, CH2), 6.30 (s, 1H, CH-chiral), 7.28 (d, J = 8.4

Hz, 2H, Ar-H), 7.36 (d, J = 8.4 Hz, 2H, Ar-H), 7.85 (s, 1H, triazole-H), 10.90 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 27.1, 28.8, 32.5, 50.2, 57.8, 107.9, 128.5, 128.9, 132.4, 140.1, 150.3, 152.6, 163.0, 193.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}ClN_5O$ 326.1116; Found 326.1121.

9,9-Dimethyl-6-(4-nitrophenyl)-6,7,8,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one (4c): Light yellow solid; Yield 96%; mp 262-264 °C; FTIR (KBr, cm^{-1}): 3285 (NH), 3070, 2958, 1672 (C=O), 1615, 1520 (NO2 asymmetric), 1348 (NO2 symmetric). ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 0.96 (s, 3H, CH3), 1.05 (s, 3H, CH3), 2.12 (d, J = 16.0 Hz, 1H, CH2), 2.31 (d, J = 16.0 Hz, 1H, CH2), 2.62 (s, 2H, CH2), 6.45 (s, 1H, CH-chiral), 7.55 (d, J = 8.8 Hz, 2H, Ar-H), 8.16 (d, J = 8.8 Hz, 2H, Ar-H), 7.88 (s, 1H, triazole-H), 11.02 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 27.0, 28.7, 32.5, 50.1, 58.0, 107.5, 123.8, 128.1, 147.2, 148.5, 150.5, 152.8, 163.2, 194.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}N_6O_3$ 337.1357; Found 337.1362.

IV. Conclusion

In conclusion, we have demonstrated that sulphanilic acid is an effective, non-toxic, inexpensive, and readily available solid acid catalyst for the synthesis of [1,2,4] triazoloquinazolinone derivatives via a one-pot three-component condensation reaction. The protocol offers multiple significant advantages, including excellent product yields (88-96%), rapid reaction times (20-45 min), mild reaction conditions, simple operational setup, and catalyst reusability up to four cycles without substantial loss of catalytic activity. This method represents a valuable, atom-economical, and environmentally friendly addition to existing methodologies for synthesizing bioactive triazoloquinazolinone heterocycles.

Acknowledgments

The authors gratefully acknowledge the Department of Chemistry and Central Instrumentation Facility (CIF), SPPU Pune for providing NMR, FTIR, and HRMS analytical testing facilities. Financial support from the University Research Grant Commission is gratefully acknowledged.

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