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Fluorite Catalysed Microwave Assisted Rapid Synthesis of Thiazolidinone Derivatives

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Abstract: *Microwave-assisted, fluorite-catalysed multicomponent reaction has been explored for the synthesis of thiazolidinone derivatives. The fluorite could efficiently influence the condensation and cyclisation through its surface properties, whereas microwave irradiation accelerates the process. The reaction proceeds rapidly to afford the desired products in excellent yields. The synthesized derivatives were characterized by ^1H NMR, and IR spectral analysis. This catalytic system could be reused up to eight times with negligible impact on overall loss in product yield.*

Keywords: Fluorite, microwave assisted synthesis, thiazolidinone, heterogeneous catalysis.

I. INTRODUCTION

Thiazolidinones represent a biologically important and structurally diverse class of five-membered heterocyclic compounds having nitrogen and sulfur atoms. These derivatives have attracted attention in the medicinal field due to the broad spectrum of pharmacological activities, making them valuable structural motifs in the development of newer therapeutic agents. These functionalized thiazolidinones have been reported as antioxidant,[1] antimicrobial,[2] HIV Inhibitor,[3] antitubercular,[4] anti-inflammatory,[5] anti-hypertensive,[6] anticonvulsant,[7] antifungal,[8] anti-hyperglycemic,[6] and antiproliferative agents[9]. In recent decades, they have been synthesized by using different methods and catalysts like, deep eutectic solvent,[10] DCC,[11] silica gel,[12] HBTU,[13] montmorilloniteK-10,[14] MCM-41supported Schiff base,[15] $CuSO_4.5H_2O$, Saccharomyces cerevisiae,[16] sulfonated mesoporous silica,[17] nano-Fe_3SO_4@SiO_2,[18] DBSA,[19] Baker's yeast,[20] and $[Et_3NH][HSO_4]$[21]. However, green chemistry approaches these reported methodologies have several limitations considering such as low yield, tedious workup procedures, very long reaction time and harsh reaction conditions. As a result, the widespread applications of these methodologies are almost restricted.

Microwave-assisted organic synthesis has emerged as an eco-friendly and efficient approach to synthesis, offering various advantages over traditional heating methods. Microwave irradiation provides uniform and rapid heating of the reaction mixture, resulting in considerably shorter reaction times and increased yields of product and selectivity.[22] This method of synthesis can also reduce consumption of solvent and energy and may proceed under solvent-free or milder reaction conditions.[23] Microwave irradiation is highly efficient for multicomponent and cyclization reactions, facilitating formation of new chemical bonds in a one-pot process rapidly.[22], [23] These valuable features make microwave-assisted synthesis an ecofriendly approach for the efficient and rapid development of structurally diverse and biologically important heterocyclic compounds.

In 2003, Wada and Suzuki explored common minerals- specifically calcite and fluorite that can act as eco-friendly heterogeneous base catalysts for the well-known Knoevenagel condensation of active methylene compounds with aryl aldehydes under solvent-free and mechanochemical conditions.[24] Considering the various heterogeneous catalytic systems employed for organic synthesis, fluorite is an attractive and relatively new inorganic catalyst due to its chemical and thermal stability, as well as its potential for catalyst recyclability. Its catalytic ability in microwave-assisted multicomponent reactions has been explored that fluorite can efficiently promote multicomponent reactions within short reaction times.[25] The combination of a recyclable fluorite catalyst with microwave irradiation is mainly appealing for the preparation of heterocyclic derivatives, where rapid condensation of reactive molecules followed by cyclization can improve synthetic efficiency.[26] However, the use of fluorite in microwave-assisted multicomponent

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strategies for the synthesis of biologically applicable heterocycles remains comparatively limited. This gives an opportunity to explore the fluorite as a catalyst for synthesizing a rapid, efficient and potentially greener synthesis of thiazolidinones. Considering the biological and medicinal importance of these thiazolidinones, we hereby report a novel multicomponent protocol catalyzed by fluorite with microwave irradiation.

II. EXPERIMENTAL

Materials and Method

All the required chemicals and reagents were commercially available and purchased from Sigma Aldrich and employed without further purification. All solvents used in this process were reagent grade. The progress of all reactions was observed by using TLC. Melting points for all synthesized thiazolidinone derivatives were measured using open capillaries tubes and are corrected. ^{1}H NMR of synthesized purified compounds were recorded on a Brucker Avance-400 MHz using $CDCl_3$ solvent. The IR spectra of all products were recorded on the Perkin Elmer FTIR 780 spectrometer. The microwave (MW) reactions were carried in CEM-908010, bench mate model, 300 W laboratory MW reactor.

III. RESULTS AND DISCUSSIONS

To optimize the reaction conditions, a model reaction was carried out under microwave irradiation by using aniline (1 mmol), benzaldehyde (1 mmol), and thioglycolic acid (1 mmol) in the presence of fluorite as the catalyst. Initially, the effect of microwave power on the multicomponent reaction was investigated by keeping constant the amounts of 1 mmol aniline, 1 mmol benzaldehyde, and 1 mmol thioglycolic acid, ethanol (5 cm^3), and fluorite (3 wt%). The reaction was studied at different power levels of microwave irradiation. The microwave irradiation power 120 W was found to be optimized quantity of power to carry out this reaction. After the optimization of the power of microwave irradiation, the amount of fluorite varied from 0 to 6 wt% with respect to the total amount of all reactants. Whereas the quantities of all reactants, ethanol, and required irradiation time were kept constant. The progress of the reaction and yield of products were compared to investigating the optimum catalyst loading. The optimum quantity of fluorite catalyst loading was found to be 2 wt%, producing an excellent yield of thiazolidinone products and ensuring maximum efficiency of the reaction.

Scheme 1: Synthesis of 1,3-thiazolidin-4-ones

Table 1: Synthesis of thiazolidinone derivatives.[a]

Entry	R^1	R^2	Product (4a-j)	Time (min)	Yield (%)[b]	Melting Point(°C) (Observed)	Melting Point (°C) (Reported)
	H	H	4a: 2,3-diphenylthiazolidin-4-one	10	95	128-130	129-131 [27]
	Me	NO_2	4b:2-(4-nitrophenyl)-3-(p-tolyl) thiazolidin-4-one	10	95	158- 160	158-160 [21]
	Cl	NO_2	4c: 3-(4-chlorophenyl)-2-(4-nitrophenyl) thiazolidin-4-one	10	95	112-115	112-115 [10]

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	Me	H	4d: 2-phenyl-3-(p-tolyl)-1,3-thiazolidinn-4-one	12	94	105-107	105-107 [27]
	OMe	H	4e: 3-(4-methoxyphenyl)-2-phenyl-1,3-thiazolidin-4-one	12	95	84-86	86-88 [21]
	Cl	H	4f: 3-(4-chlorophenyl)-2-phenylthiazolidin-4-one	10	93	120- 122	121-123 [10]
	F	H	4g: 3-(4-flurophenyl)-2-phenyl-1, 3-thiazolidin-4-one	10	94	117- 119	122-126 [10]
	H	Cl	4h: 2-(4-chlorophenyl)-3-phenyl-1, 3-thiazolidin-4-one	10	95	123-126	122-126 [10]
	H	Me	4i: 3-phenyl-2-(p-tolyl) -1, 3-thiazolidin-4-one	10	94	123-126	116-118 [10]
	H	OMe	4j: 2-(4-methoxyphenyl)-3-phenyl-1, 3-thiazolidin-4-one	12	95	99-101	97-99 [10]

[a]Reaction conditions: 1 mmol aniline (1a), 1 mmol benzaldehyde (2a), 1 mmol thioglycolic acid (3), ethanol (5 cm^3), and fluorite (2 wt%) at 120 W microwave irradiation. [b]Isolated yield.

Under the optimized condition of catalyst loading and microwave irradiation power 120 W, the model reaction afforded the desired thiazolidinone product in 10 minutes. A reaction time of 10–12 minutes was found to be sufficient for the conversion of the reactants, producing the desired products in 93–95% yields. The optimum irradiation time 120W was selected based on maximum yield of the product and consumption of the starting materials, as monitored by TLC. The crude products were extracted and purified. The explored fluorite catalyst was separated from the reaction mixture after completion of the reaction and reused for at least eight consecutive cycles, exhibiting its potential for recyclability. The synthesized derivatives were characterized by ^{1}H NMR and IR spectrometric analyses.

Synthesis of 1,3-thiazolidin-4-ones

A mixture of 1 mmol aniline, 1 mmol benzaldehyde and 1 mmol thioglycolic acid dissolved in 5 cm^3 of 95 % ethanol and Fluorite (2wt %) was taken in a funnel caped conical flask and irradiated under microwave irradiation at 120W. The reaction process was monitored by TLC. Following completion of the reaction, the mixture was allowed to cool, and the crude reaction product was extracted and further refined by recrystallisation method.

Representative spectral data

4a: *2,3-diphenylthiazolidin-4-one*: Yield: 95 %; Colour-white solid; Melting point 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 9.8, 4.8 Hz, 7H), 7.20 (d, J = 7.9 Hz, 3H), 6.18 (s, 1H), 3.98 (dd, J = 50.1, 15.8 Hz, 2H). FTIR (cm^{-1}): 2930, 1673, 15880, 1486, 1340, 605.

4b: *2-(4-nitrophenyl)-3-(p-tolyl) thiazolidin-4-one*: Yield: 95 %; Yellow solid; Melting point: 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.16 – 6.88 (m, 4H), 6.33 (s, 1H), 3.88 (dd, J = 36.7, 15.9 Hz, 2H), 2.34 (s, 3H). FTIR (cm^{-1}): 2938, 1688, 1513, 1386, 1272, 624.

4c: 3-(4-chlorophenyl)-2-(4-nitrophenyl) thiazolidin-4-one: Yield: 95%; White solid; Melting Point:113-115 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.21 (dd, J = 9.6, 4.9 Hz, 7H), 7.13 (d, J = 7.9 Hz, 3H), 6.18 (s, 1H), 3.97 (dd, J = 50.1, 15.8 Hz, 2H). FTIR (Cm^{-1}): 3058, 1670, 1528, 1489, 1377, 827, 726,701.

IV. CONCLUSION

In conclusion, rapid and efficient microwave-assisted multicomponent reaction protocol has been established for the preparation of thiazolidinone derivatives by using fluorite as a heterogeneous catalyst. The synergetic use of fluorite and microwave irradiation provided the desired products in excellent yields within 10-12 minutes under mild reaction conditions. This methodology offers catalyst recovery and reuse, operational simplicity, and convenient isolation of products. The use of an easily available fluorite as an inorganic catalyst along with microwave irradiation provides a newer approach for promoting multicomponent condensation–cyclization reactions and contributes to the development of rapid and more efficient and greener synthetic methodologies for relevant heterocyclic compounds.

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