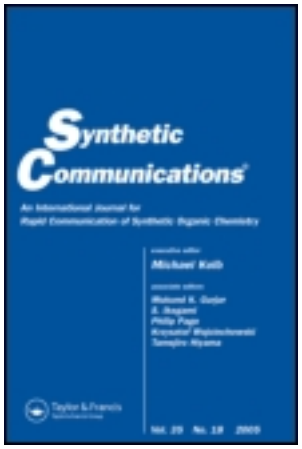

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Microwave-Assisted One-Pot Synthesis of Bioactive UGI-4CR Using Fluorite as Benign and Heterogeneous Catalyst

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MICROWAVE-ASSISTED ONE-POT SYNTHESIS OF BIOACTIVE UGI-4CR USING FLUORITE AS BENIGN AND HETEROGENEOUS CATALYST

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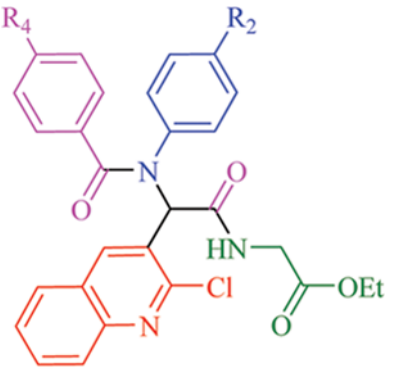
GRAPHICAL ABSTRACT



5 (a-h)

Abstract *Fluorite has been used as an activating heterogeneous catalyst for a rapid and facile one-pot synthesis of biologically active Ugi four-component reaction (Ugi-4CR) under microwave irradiation in good to moderate yields with short reaction times. The catalyst is environmentally benign, commercially available, and reusable several times with no reduction in its efficiency. The resulting Ugi derivatives* ***5(a–h)*** *were characterized on the basis of* ^{1}H *and* ^{13}C *NMR, infrared, elemental analysis, and mass spectral data. The synthesized moieties were screened for their potential antibacterial activities in vitro against a few microorganisms: Staphylococcus aureus (Gram positive), Bacillus subtilis (Gram positive), Escherichia coli (Gram negative), and Proteus vulgaris (Gram negative). The screening data show that compounds* ***5a, 5c, 5e,*** *and* ***5h*** *are highly active against the strains.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

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Keywords Biological activity; fluorite; green synthesis; heterogeneous catalysis; microwave irradiation; Ugi-4CR

INTRODUCTION

The utility of microwave (MW) energy in synthetic organic chemistry has been increasingly recognized in recent years.[1] Microwave-assisted solid-phase heterogeneous reactions are environmentally benign methodologies that have greater selectivity, enhanced reaction rates, cleaner products, and manipulative simplicity.[2] Microwave-mediated multicomponent reactions constitute an especially attractive synthetic strategy for rapid and efficient library generation because products are formed in a single step and diversity can be achieved simply by varying the reacting components.[3]

Among many kinds of multicomponent condensations, the Ugi reaction[4] is highly convergent for the rapid generation of organic druglike molecule libraries and many different types of biologically active targets.[5] The Ugi-4CR in which an amine, an aldehyde or ketone, a carboxylic acid, and an isocyanide combine to yield α-*N*-acylaminoamide[6] is particularly attractive because of the wide range of products obtainable through variation of the starting materials. The quinoline nucleus is present in several natural compounds and pharmacologically active substances displaying a broad range of biological activity. Quinolines and their derivatives have been found to possess anti-inflammatory,[7] antimalarial,[8] antimicrobial,[9] anticonvulsant,[10] antineoplastic,[11] vasorelaxing,[12] and antiproliferative[13] activities. Ugi four-component derivatives have also been found to have various applications (viz., anesthetics, antibiotics, natural product isolation, HIV protease inhibitor crixivan,[14–16] etc.). Therefore, it is of significance to develop novel preparations for Ugi-4CR having a quinoline nucleus.

Classically, the Ugi reaction was performed at room temperature or under reflux in methanol with reaction times up to 12–24 h or more using several catalysts.[17–20] However, most of these methods employ long reaction times with moderate yields. Recently, a new, simple, and elegant synthesis of Ugi-4CR has been described using ionic liquids and water.[21,22] Moreover, fluorite has also been used as a mild and efficient promoter for various organic reactions.[23,24] Fluorite[25,26] (also called fluorspar) is a naturally occurring halide mineral composed of calcium fluoride (CaF_2). Fluorite is the primary source of fluorine and its compounds. It has a hardness of 4 on Mohs's scale and a melting point of 1360 °C. However, this rock mineral is an intrinsically acidic substance, but it cannot be used in solution chemistry bacause of its insolubility in organic solvents and water. In view of the remarkable importance from pharmacological, industrial, and synthetic points of view, herein we report that fluorite acts as a heterogeneous mild acid catalyst for the one-pot synthesis of biologically active Ugi-4CR under a microwave method within the framework of green chemistry protocol. Fluorite is environment benign, reusable, and commercially available.

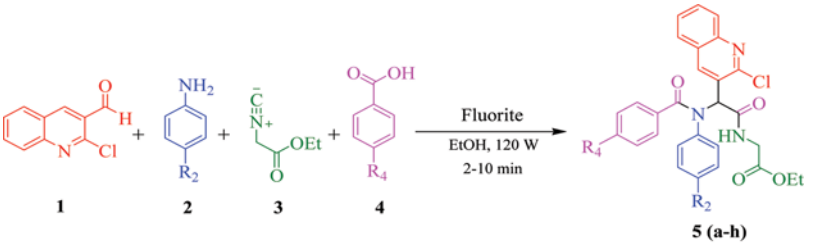
RESULTS AND DISCUSSION

In the present study, we report the condensation of 2-chloroquinoline-3-carbaldehyde, substituted aniline, ethylisocyanoacetate, and an aromatic carboxylic acid via a microwave method in the presence of fluorite as a catalyst (Scheme 1). The

reaction initiates with the formation of imine from amine and aldehyde with loss of 1 equivalent of water. Proton exchange with carboxylic acid activates the iminium ion for nucleophilic addition of the isonitrile with its terminal carbon atom to nitrilium ion. A second nucleophilic addition takes place at this intermediate with the carboxylic acid anion. The final step is a Mumm rearrangement with transfer of the acyl group from oxygen to nitrogen. All steps in the reaction are reversible except the Mumm rearrangement, which drives the whole reaction sequence. Although we have synthesized Ugi-4CR derivatives with 2-chloroquinoline-3-carbaldehyde, substituted aniline, ethylisocyanoacetate, and an aromatic carboxylic acid, these sequences of reaction can also be performed with various aliphatic as well as aromatic aldehydes. A majority of the variations can also be made at the carboxylic acid and primary amine center, whereas only a few combinations of educts do not react. Ugi-4CR can also proceed using various isonitriles.[27]

Fluorite acts as a mild acid in the dehydration reaction and increases the reaction rate without affecting the yield of desired products. The results of model reaction (Scheme 1) pertaining to yield and reaction times are summarized in Table 1. It is significant from Table 1 that the catalytic amount of fluorite accomplishes the reaction successfully and the use of microwave energy further enhances the yield of the product with reduction in time. Consistent yields of 70–95% were obtained in 2–10 min of microwave irradiation in a green chemistry protocol.

The integral part of this study is to synthesize Ugi-4CR using fluorite as a catalyst; we therefore study the activity of fluorite by comparing three reactions in the presence of catalyst and same reactions in the absence of catalyst. The reactions were



	R_2	R_4
5a	p-Cl	p-NO_2
5b	p-Me	p-Cl
5c	p-OMe	p-NO_2
5d	p-NO_2	p-NH_2
5e	p-OMe	p-Me
5f	p-Me	p-NH_2
5g	p-OMe	p-Cl
5h	p-NO_2	p-Me

Scheme 1. Synthesis of Ugi-4CR derivatives using fluorite under MW irradiation. (Figure is provided in color online.)

Table 1. Time and % yield of Ugi-4CR derivatives using fluorite (2% wt) under MW irradiation

Compounds	Time (min)	% Yield[a]	M.P (°C)
5a	3	92	178–180
5b	6.5	89	168–172
5c	2	95	158–160
5d	7.5	88	173–175
5e	4.5	91	142–145
5f	2.5	90	160–162
5g	10	89	153–155
5h	5	90	164–166

[a]Isolated yields after recrystallization.

performed via microwave using 3-nitrobenzaldehyde, aniline, methylisocyanoacetate, and a sequence of primary, secondary, and tertiary aliphatic carboxylic acid in similar reaction conditions. The results are tabulated in Table 2. Consistent decrease in yields and increase in reaction time were observed in the presence as well as in the absence of the catalyst for primary, secondary, and tertiary aliphatic acids respectively. Although fluorite is an excellent catalyst, moderate yields have been obtained. This is possibly due to aliphatic carboxylic acids.[28] In the case of aliphatic acids, electron-donating alkyl groups are present, which do not allow carboxylic acid to donate its proton easily and ultimately lead to the decrease in the formation of the carboxylate ion. In aromatic acids, benzene ring is an electron-withdrawing compound and the carboxylic acid easily donates its proton and forms carboxylate ion, which is a good nucleophile.

To check the efficiency of the catalyst, we have synthesized compound **5c** in three consecutive reactions using various amounts of catalyst as 2% and 2.5% weight with respect to all reactants. Fluorite was crushed into pieces 1–2 mm in size before use, frequently washed with distilled water and acetone, and dried. Efficient recyclability was observed in three consecutive reactions and the desired product was obtained in the stipulated time period. No change in the yields and purity of the desired product was observed (Table 3). It is noteworthy that the catalyst was easily isolated after the completion of reaction and reused several times. All synthesized compounds were evaluated by ^{1}H NMR, ^{13}C NMR, infrared, elemental analysis, and mass spectral data.

Table 2. Comparative study of Ugi-4CR with and without fluorite catalyst (2% wt) under MW irradiation

		Catalyst		No catalyst	
Entry	Carboxylic acids	Time (min)	%Yield[a]	Time (min)	%Yield[a]
1	Acetic	14	70	30	62
2	Isobutyric	18	66	45	53
3	Pivalic	25	58	120	40

[a]Isolated yields after recrystallization.

Table 3. Recycling experiments of catalytic activity of fluorite using compound **5c**

Catalyst (wt %)	Cycle	Time (min)	%Yield[a]	Recovery (wt %)
2	1	2	95	97
	2	2	93	97
	3	2	94	98
2.5	1	2	90	96
	2	2	92	98
	3	2	95	97

[a]Isolated yields after recrystallization.

ANTIBACTERIAL ACTIVITY

The synthesized compounds **5(a–h)** were screened for antibacterial activities against *S. aureus*, *B. subtilis*, *E. coli*, and *P. vulgaris* using the well diffusion method. Each test compound (5 mg) was dissolved in ethanol (5 ml, 1000 μg/ml), which was used as sample solution. Sample size for all the compounds was fixed at 0.1 ml. Ampicillin and streptomycin were used as standard drugs, and ethanol was used as negative control. The cultures of the bacterial strains were inoculated in 10 ml nutrient broth and incubated at 37 °C for 24 h. The Petri dishes and nutrient agar medium were sterilized by autoclaving. To this sterilized nutrient medium 1 ml of one-day-old bacterial culture was added and spread over the Petri plate. The wells impregnated with 1000 μg/ml of newly synthesized compounds were introduced aseptically in the nutrient agar plate. All the nutrient agar plates were incubated at 37 °C for 24 h, after which the plates were observed for clear zone of inhibition. The screening results from Table 4 indicate that the compounds **5a, 5c, 5e,** and **5h** showed excellent antibacterial activities, whereas **5b, 5d, 5f,** and **5g** show moderate to negligible activity against the used strains.

Table 4. Antibacterial activity of Ugi-4CR derivatives **5 (a–h)**

	Gram-positive bacteria		Gram-negative bacteria	
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. vulgaris*
5a	+++	+++	+++	++
5b	++	+	++	—
5c	+++	+++	++	++
5d	+	+	++	+
5e	+++	++	+++	+++
5f	++	—	+++	+
5g	++	+	+	++
5h	+++	++	+++	+++
Ampicillin	+++	++	+++	++
Streptomycin	+++	+++	+++	+++

Key to symbols: Inactive = —(inhibition zone < 5 mm); Slightly active = +(inhibition zone 5–10 mm); Moderately active = ++ (inhibition zone 10–15 mm); Highly active = +++ (inhibition zone > 15 mm).

EXPERIMENTAL

All reagents and solvents are of analytical grade and were used directly. All melting points were determined by the open-tube capillaries method and are uncorrected. The microwave (MW) reactions were carried out in a CEM 908010, bench mate model, 300-W laboratory MW reactor. IR spectra (υ_{max} in cm^{-1}) were recorded on Schimadzu-IR Prestige 21 spectrophotometer using the KBr technique. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-Avance (400-MHz) spectrophotometer using dimethylsulfoxide (DMSO-d_6) solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Waters Micromass Q-T microspectrometer. The elemental analysis (C, H, and N) of compounds was performed on a Carlo Erba-1108 elemental analyzer. Antibacterial screening was carried out at the Department of Biotechnology, Sindhu Mahavidyalaya, Nagpur, India.

A mixture of 2-chloroquinoline-3-carbaldehyde (0.01 mol), substituted aniline (0.01 mol), ethylisocyanoacetate (0.01 mol), and aromatic carboxylic acid (0.01 mol) was dissolved in 5 ml of 95% ethanol and the catalyst, fluorite (2% weight with respect to all reactants), was taken in a conical flask capped with a funnel and irradiated under microwave at 120 W (Scheme 1). The completion of the reaction was monitored by thin-layer chromatography (0.5 mm thick) using silica gel-G–coated Al plates (Merck) by using a mixture of ethyl acetate and hexane as mobile phase, and spots were visualized by exposing the dry plates in iodine vapors. After completion, the reaction mixture was allowed to attain room temperature. The crude product and catalyst was collected by filtration. The crude product was purified by recrystallization from hot ethanol.

CONCLUSION

In conclusion, this study shows that fluorite is an excellent heterogeneous mild acid catalyst for one-pot microwave-mediated synthesis of biologically active Ugi-4CR, thereby reducing reaction time with good to excellent yields in a green chemical pathway. Furthermore, utility, no toxicity, reusability, low cost, and ease of isolation after completion of reaction are the remarkable features of the catalyst.

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