Fluorite Catalyzed Ultrasound Promoted Passerini Reaction

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Abstract

In the present article, we describe a series of novel one-pot synthesis of three-component Passerini reaction combining an aldehyde, carboxylic acid and an isonitrile using ultrasonication. The reaction was catalyzed by natural fluorite. The products were obtained in good yields of about 65-90% in 120-160 min. The structures were confirmed from spectroscopic analysis such as IR, ^{1}H NMR and Mass spectra. The derivatives **4 (a-e)** were screened for their potent *in vitro* antibacterial activity using few Gram-positive and negative bacteria against a reference antibiotic, Amoxicillin. All the synthesized compounds have shown significant potency when compared with reference drugs. Compounds **4a** and **4b** were proved to be equipotent compared to Amoxicillin. The significant aspects of our methodology were efficiency, generality, high yield, short reaction time, low cost, ease of product isolation, use of reusable catalyst, use of alternative source of energy and conformity with the green chemistry protocols.

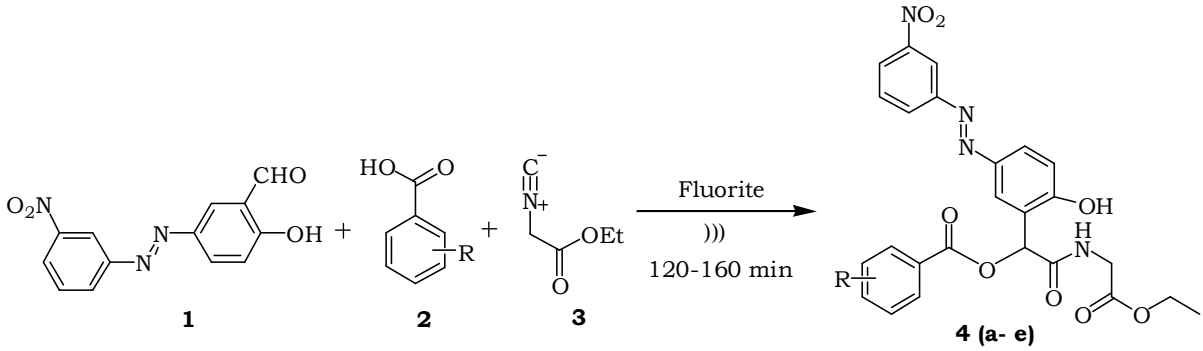
Keywords: Antibacterial, Fluorite, Green synthesis, Passerini reaction, Ultrasound.

Introduction:

Isocyanide-based multicomponent reactions are used extensively in target oriented and diversity oriented organic synthesis [1, 2]. The most widely known and best characterized isocyanide-based multicomponent reaction is the Passerini three-component reaction (P-3CR). It is the first isocyanide based multi-component reaction developed, and currently plays a central role in combinatorial chemistry [3]. In the Passerini 3CR, an isocyanide, a carboxylic acid, and either an aldehyde or a ketone react with one another to yield α-acyloxycarboxamide, which has wide applications in combinatorial synthesis [4].

Ultrasound has found a variety of uses in engineering, science and medicine. The use of ultrasounds in organic transformations enhance reaction rates and yield of reactions and in several cases facilitates organic transformation at ambient conditions which otherwise require drastic conditions of temperature and pressure [5, 6]. Ultrasonic irradiation leads to the acceleration of numerous catalytic reactions in homogeneous and heterogeneous systems [7]. Furthermore, significant improvements can be realized with respect to the yields [8, 9].

Herein, we wish to report an efficient and facile synthesis of P-3CR catalyzed by natural fluorite [10] using ultrasound technology. All the synthesized derivatives were further screened for their biological application using Amoxicillin as reference drug.



R = 4-NH_2, 4-OH, 4-NO_2, 4-Cl, 4-OCH_3

Scheme 1 Ultrasound promoted P-3CR using Fluorite catalyst

Material and Methods:

All reagents and solvents used are of analytical grade and purchased from a commercial source and used directly. The reaction was carried out in Spectra lab model UCB 40D Ultrasonic cleaner. The purity of compounds was checked by Thin-Layer Chromatography, TLC (0.5 mm thickness) using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapors. IR spectra (ν_{max} in cm^{-1}) were recorded on a Schimadzu-IR Prestige 21 spectrometer using KBr technique. ^1H NMR spectra were recorded on a Bruker-Avance II (400 MHz), spectrophotometer using DMSO-d_6 solvent and TMS as an internal standard. Mass spectra were recorded on a Micromass Q–T of high-resolution mass spectrometer.

Protocol for *in vitro* antimicrobial screening

All the synthesized compounds **4 (a-e)** were screened against *Staphylococcus aureus and Bacillussubtilis* (Gram-positive), *Escherichia coli* and *Klebsiellapneumoniae* (Gram-negative) using well diffusion method. The cultures of bacterial strains were inoculated in 10 ml nutrient broth and incubated at 37°C for 24 hrs. Amoxicillin was used as standard drug and ethanol as negative control. 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. The Petri dishes and nutrient agar medium was 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 1000µg/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 hrs after which the plates were observed for clear zone of inhibition.

Protocol for ultrasound promoted synthesis of P-3CR4 (a-e)

A mixture of 2-hydroxy-4-((3-nitrophenyl)diazenyl)benzaldehyde(0.01 mol) **1**, aromatic carboxylic acid (0.01 mol) **2** and ethylisocyanoacetate (0.01 mol) **3** was dissolved in 10 ml of 95% ethanol in one-pot. The reaction mixture was irradiated in water bath of an ultrasonic cleaner for the period 120-160 min in presence of Fluorite as catalyst (2% weight with respect to all reactants) **Scheme 1**. The completion of the reaction was monitored by TLC by using mixture of ethyl acetate

and hexane as mobile phase. After completion, the reaction mixture was poured into crushed ice. The crude product and catalyst was collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. The following are the spectral data of the synthesized compounds.

(E)-2-(2-ethoxy-2-oxoethylamino)-1-(2-hydroxy-5-((3-nitrophenyl)diazenyl)phenyl)-2-oxoethyl4-aminobenzoate (**4a**)

Yield: 90%; IR (KBr): 3410 (-OH), 3320 (-NH), 3011 (Ar-H), 1645 (-C=O), 1530 (-NO_2), 1428 (-N=N).^{1}H NMR: 6.57-8.39 (m, 11H, Ar-H), 6.19 (s, 1H, -CH), 5.12 (s, 1H, -OH), 4.21 (d, 2H, -CH_2), 4.12 (q, 2H, -CH_2), 2.81 (s, 1H, -NH), 1.38 (t, 3H, -CH_3). MS: $C_{25}H_{23}N_5O_8$: m/z: 521.15 (M^+, 100%).

(E)-2-(2-ethoxy-2-oxoethylamino)-1-(2-hydroxy-5-((3-nitrophenyl)diazenyl)phenyl)-2-oxoethyl4-hydroxybenzoate (**4b**)

Yield: 88%; IR (KBr): 3400 (-OH), 3300 (-NH), 3020 (Ar-H), 1640 (-C=O), 1536 (-NO_2), 1420 (-N=N).^{1}H NMR: 6.58-8.43 (m, 11H, Ar-H), 6.19 (s, 1H, -CH), 5.18 (s, 1H, -OH), 5.0 (s, 1H, -OH), 4.24 (d, 2H, -CH_2), 4.16 (q, 2H, -CH_2), 2.73 (s, 1H, -NH), 1.39 (t, 3H, -CH_3). MS: $C_{25}H_{22}N_4O_9$: m/z: 522.14 (M^+, 100%).

(E)-2-(2-ethoxy-2-oxoethylamino)-1-(2-hydroxy-5-((3-nitrophenyl)diazenyl)phenyl)-2-oxoethyl4-nitrobenzoate (**4c**)

Yield: 78%; IR (KBr): 3415 (-OH), 3322 (-NH), 3026 (Ar-H), 1647 (-C=O), 1543 (-NO_2), 1432 (-N=N).^{1}H NMR: 6.55-8.35 (m, 11H, Ar-H), 6.19 (s, 1H, -CH), 5.11 (s, 1H, -OH), 4.27 (d, 2H, -CH_2), 4.18 (q, 2H, -CH_2), 2.76 (s, 1H, -NH), 1.36 (t, 3H, -CH_3). MS: $C_{25}H_{21}N_5O_{10}$: m/z: 551.13 (M^+, 100%).

(E)-2-(2-ethoxy-2-oxoethylamino)-1-(2-hydroxy-5-((3-nitrophenyl)diazenyl)phenyl)-2-oxoethyl4-chlorobenzoate (**4d**)

Yield: 72%; IR (KBr): 3400 (-OH), 3315 (-NH), 3000 (Ar-H), 1640 (-C=O), 1535 (-NO_2), 1431 (-N=N).^{1}H NMR: 6.59-8.45 (m, 11H, Ar-H), 6.19 (s, 1H, -CH), 5.18 (s, 1H, -OH), 4.26 (d, 2H, -CH_2), 4.15 (q, 2H, -CH_2), 2.83 (s, 1H, -NH), 1.38 (t, 3H, -CH_3),. MS: $C_{25}H_{21}ClN_4O_8$: m/z: 540.10 (M^+, 100%).

(E)-2-(2-ethoxy-2-oxoethylamino)-1-(2-hydroxy-5-((3-nitrophenyl)diazenyl)phenyl)-2-oxoethyl4-methoxybenzoate (**4e**)

Yield: 65%; IR (KBr): 3416 (-OH), 3331 (-NH), 3023 (Ar-H), 1645 (-C=O), 1427 (-N=N), 1538 (-NO_2).^{1}H NMR: 6.59-8.37 (m, 11H, Ar-H), 6.19 (s, 1H, -CH), 5.12 (s, 1H, -OH), 4.20 (d, 2H, -CH_2), 4.12 (q, 2H, -CH_2), 3.73 (s, 3H, -OCH_3), 2.85 (s, 1H, -NH), 1.31 (t, 3H, -CH_3). MS: $C_{26}H_{24}N_4O_9$: m/z: 536.15 (M^+, 100%).

Results and Discussion:

In continuation of our ongoing research on multicomponents,2-hydroxy-4-((3-nitrophenyl)diazenyl)benzaldehyde has been prepared in our previously reported work [11], which has been condensed in P-3CR as compound **1**. P-3CR was atom-economical which proceeds through acyl transfer and amide tautomerization thereby producing the final product. Lewis acid and Lewis base have been used to

promote the Passerini reaction that is why fluorite was used as catalyst which acts as Lewis acid in the reaction. The catalyst can be easily collected after the completion of the reaction and was benign, efficient and reusable. Higher yields were achieved in satisfactory reaction time. The structures were confirmed from IR and ^{1}H NMR spectroscopic data and were found to be in well agreement with the assigned structures. The mass spectra of these compounds displayed a molecular ion peak at their respective m/z values which are corresponding well with the respective molecular mass.

The screening results of *in vitro* antibacterial activity showed a broad spectrum for compounds **4a**and **4b** when compared with Amoxicillin. On the contrary, compounds **4c, 4d** and **4e** showed moderate activity against the used strains. The results were described in **Table 1**. On the basis of screening data obtained from *in vitro* studies, we have concluded that the synthesized moieties are equipotent antibacterial agents.

Table 1 Antibacterial screening data of compounds 4 (a-e)

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
4a	+++	++	+++	+++
4b	+++	+++	++	++
4c	++	+	+	++
4d	++	+	++	++
4e	++	++	++	+
Amoxicillin	+++	+++	+++	+++

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).

Conclusions:

We have developed an efficient and eco-friendly synthesis for the development of drug-like targets using P-3CR through green technology of ultrasonication. Fluorite used was commercially available and benign catalyst. Antibacterial screening results revealed that compounds **4a** and **4b** were found to be equipotent and other derivatives were also active against bacterial strains used with respect to Amoxicillin.

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