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Smart Approach for Multicomponent Hantzsch Condensation Reaction under Solvent-Free Condition

Suchita Gadekar[a], Suryakant Sapkal[b], Ramesh Shingare[a], BalajiMadje[a]*

[a]*Department of Chemistry VasantraoNaik College, Aurangabad-431003, India.*

[b]*Department of Chemistry, Jawaharlal Nehru Engineering College, Aurangabad-431 004, India.*

Corresponding author Dr. BalajiMadjeEmail:- drmadjebr@rediffmail.com*

Abstract: synthesis of Polyhydroquinoline derivatives via multicomponent reaction of aromatic aldehydes, dimedone, ethyl acetate and ammonium acetate in the presence of organocatalyst 3-morpholinopropane-1-sulfonic acid (MOPS) under microwave irradiation have been demonstrated. This catalyst offers various benefits as it works at near-neutral pH with a pKa of 7.20 forming a set of derivatives in shorter reaction times with moderate to good yields.
Key Words: organocatalyst, multicomponent reaction, MOPS, microwave irradiation

1. Introduction

Nowadays time has come to expand horizon of our conscious foresight about environmental consequences and side effects. It is expected from all the chemists and co-workers while performing any chemical transformations in the laboratory. This is because, no any chemical compound is environment friendly. Therefore chemists has either to modify the protocols or keep control on it, so that the developed methodology can help to protect human health and maintains environment unaffected [1].

Polyhydroquinolinemol ecules through multicomponent reactions have been attracted attention of chemists and pharmacists because of theirbroad spectrum of medicinal activity and its usesas precursor for active pharmaceutical ingredient (API)such as excellent antibacterial, antifungal and equipotent activity, Ca^{2+}channel blockers, antidiabetic,

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antitumor, vasodilator,hepatoprotective,anticancer,agains HIV infection and other various diseases[2-6].

Keeping these factors in view, it was thought worthiness to synthesize various polyhydeoquinoline moieties by means of non-conventional techniques. More preferentially organocatalyst MOPS, are found to be smart and compatible under microwave irradiation reaction conditions with variety of substrates.

Beforehand there are several reports established in a database even though scope is remarkable to work on the same. Few noteworthy of them are, cericammonium nitrate (CAN) at room temperature undersolvent-free condition [2], supported ZnOnanoparticals [7], using silica sulphuric acid as aheterogeneous catalyst [8],3-methyl-1-sulfonic acid imidazolium chloride ([Msim]Cl) [6], Mesoporous vanadium ion doped titania nanoparticles (V–TiO_2)undersolvent-free condition[9], $BiFeO_3$ Magnetic Nanoparticles [10],nano-SnO_2under reflux condition [11] and more by mean of conventional and non-conventional [12-14].

2. Result and Discussion:

In continuation of our efforts to establish smart protocol towards multicomponent reaction herein, we have attempted to synthesize targeted product polyhydroquinoline**5** by cyclocondensation of benzaldehyde**1**, ethyl acetoacetate **2**,dimedone**3**, and ammonium acetate**4** under microwave irradiation at moderate mode in the presence of optimal concentration of MOPS as a catalyst (**Scheme 1**).

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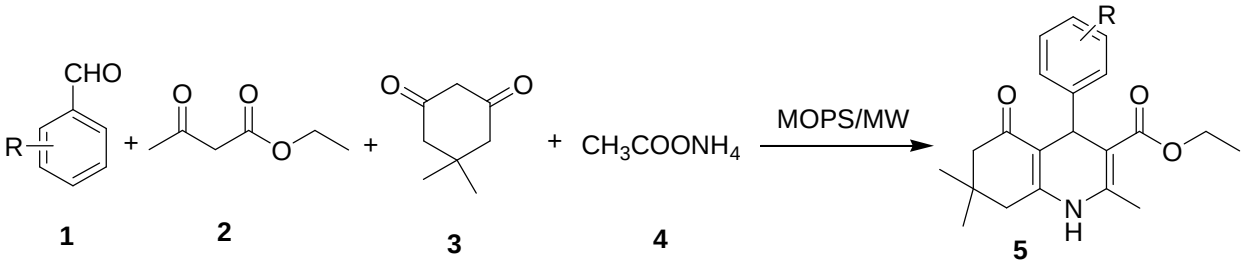

Scheme 1: Synthesis of Polyhydroquinoline derivatives using MOPS.

During reaction screening pale yellow coloration is observed after 2 minutes irradiation. It seems that formation of imine intermediate. Which on continuous irradiation at constant power mode we get targeted product withineight minutes mean while we homogenized reaction mixture with the help of glass road after each one minute.

Catalytic concentration has been optimized for the model reaction (**Scheme 1**) by taking stoichiometric measurement in mole % of MOPS such as 4, 8, 12, 16, 18 etc. It has been experimentally observed that 14 mole % catalyst is competent to produce maximum yield of the product (**Table 1**).

Table 1: Optimization of catalyst concentration for model reaction.

Sr. No	Mole %	Time (Min)	Yield %	
1	4	30	55	
2	8	25	60	
3	12	10	68	
4	14	8	89	
5	16	8	90	

To explore more results we extended developed methodology for further derivatization with substituted aromatic aldehydes. We are delighted to note that all the derivatives were synthesized smoothly within stipulated time period even with electron withdrawing and repelling substituents didn't show remarkable difference in reaction time and yield of the product (**Table 2**).

Sr. No[a]	R	Time (min)	Yield[b]	M.P. (°C)
1	H	8	89	201-203
2	2-Cl	7	86	207-209
3	4-Cl	7	86	245-247
4	3-OH	8	68	220-222

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5	4-OH	7.5	82	231-233
6	4-CH_3	6	74	262-264
7	4-OH, 3-OCH_3	6	89	211-213
8	4-N $(CH_3)_2$	7	89	228-230
9	3-NO_2	9	66	173-175
10	4-NO_2	8	69	241-243

[a]All products were characterized from their spectroscopic (IR,[1]H NMR, and MS) data and compared with authentic samples.[b]Isolated yields.

3. Experimental:

*General experimental procedure:*A mixture of aromatic benzaldehyde (0.221g,0.002mol), Ethyl acetoacetate (0.260g, 0.002mol), dimedone (0.280g,0.002mol),ammonium acetate (0.231, 0.003mol)and MOPS (14 mol%) were taken in a beaker. The reaction mixture homogenized with the help of glass rod and irradiated in microwave oven (Medium mode) by the interval of 20 second. The progress of reaction was monitored on TLC. After completion of the reaction, mixture was cooled to room temperature and poured on crushed ice. Thus, solid obtained was filtered, dried and purified by crystallization in ethanol. *Spectral analysis of representative compound*: (**Table 2, Sr. No 1**): Yellow solid. m.p.= 201-203°C. ^{1}HNMR (300 MHz, $CDCl_3$): δ= 0.90 (s, 3H, CH_3), 1.10 (s, 1H, CH_3), 1.79(s, 3H, CH_3,), 1.22-1.28 (t, 3H, CH_3), 2.20 (s, 2H, CH_2), 3.01 (s, 2H, CH2), 3.95-4.05 (q, 2H, CH2), 50.5 (s, 1H), 6.78 (s, 1H, NH), 7.6-7.29 (m, 5H, Ar); EI-MS (%): m/z = 340.10 (M^{+1}).

4. Conclusions:

We have developed a smart, beneficent and user friendly synthetic protocol for pharmacodynamic polyhydroquinoline derivatives favored by gracious catalyst MOPS under microwave irradiation. This synthetic strategy also covers the advantages of one-pot multicomponent transformations which will make this research work practical and economically feasible and provides insight for sustainability.

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