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Microwave Assisted, L-Tyrosine Catalyzed Efficient Synthesis of Tetrahydrobenzo[b] Pyrans

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ABSTRACT

A mild and efficient protocol has been developed for the synthesis of Tetrahydrobenzo[b]pyrans, from aldehyde, malononitrile and dimedone in presence of L-Tyrosine under Microwave irradiation. High yield, simple workup procedure and mild reaction condition are main feature of this protocol.

Keywords: Microwave, L-Tyrosine, Tetrahydrobenzo[B]Pyrans, Multicomponent Reaction.

I. INTRODUCTION

Pyran derivatives are one of the most common compounds present in various biologically active natural and synthetic products[1]. Among them, functionalized chromenes (benzopyrans) are also an important class of compounds, which constitute the structural unit of series of biologically active natural products and drugs[2]. Chiefly, among various chromene derivatives, Tetrahydrobenzo[b]pyranswithcyano-functionality have potential applications in the treatment of rheumatoid, psoriasis, and cancer[3]. Other properties such as laser dyes[4], optical brighteners[5], fluorescence markers[6], pigments[7], cosmetics, and potent biodegradable agrochemicals[8] are well known for decades. In addition chromenes have been used for the treatment of numerous neurodegenerative diseases, which include Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS associated dementia and Down's syndrome and also used in the treatment of schizophrenia and myoclonus[9]. Antihypertensive and anti-ischemic behavior has been exhibited by aminochromene derivatives[10] and other substituted chromenes encourage apoptosis in tumor cells by binding to the Bcl-2 protein[11].The currentinterest in Tetrahydrobenzo[b]pyranderivativefor the treatment of human inflammatory TNFa-mediated diseases, such as psoriatic arthritis and rheumatoid and in cancer therapy[12].

A literature studyrevealed that Tetrahydrobenzo[b]pyranswith nitrile and amino functions at the 3 and 2 positions,are known to possess diverse pharmaceutical properties, such as cytotoxic, antioxidant, anti-bacterial, anti-proliferative, anti-microbial, anti-HIV, anti-rheumatic, anti-cancer activities[13].Because of increasing environmental concerns, the development of a clean synthetic procedure has become crucial and demanding research. Organic synthesis, experienced thoughtful changes in recent years with more sustainable processes that avoid the extensive use of toxic and hazardous solvents and reagents, vigorous reaction conditions, costly and complicated catalytic systems[14].

MW irradiation has emerged as an effective heating source for organic synthesis due to shorter reaction times, uniform and selective heating, higher yields, cleaner reactions, easy work up[15].

We have selected L-tyrosine organo catalyst for this purpose. In this sense Microwave-assisted organic synthesis has become a significant tool for accelerating drug discovery and development processes. The choice of L-tyrosine is based on the fact that it is an efficient, bi-functional, zwitterionic and eco-friendly organocatalyst capable of playing multiple catalytic roles as an acid and base.its catalytic activity in various organic transformations is till unnoticed. Very few report of the catalytic ability of L-tyrosine is reflected, such as Bigenelli reaction[16],Knoevenagel condensation reaction under grindstone [17].Recently

AnamikaKhaskelet al. used L-Tyrosine loaded nanoparticle for the synthesis of Biscoumarin and Hantzschdihydropyridines[18].

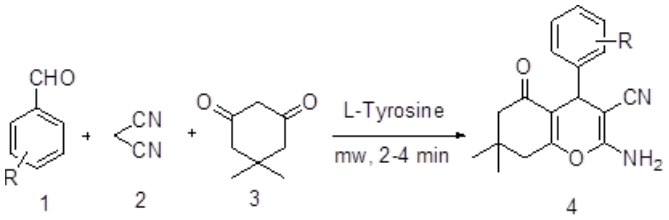
II. EXPERIMENTAL

A. Materials and Apparatus

All chemical and reagents are purchased from SD Fine chemical company with high purity and used without further purification. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus. Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer spectrum 65 FT-IR spectrometer. ^{1}H NMR spectra were recorded on an 400 MHz FT-NMR spectrometer in DMSO or $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. The microwave irradiation was carried out in a scientific microwave oven (CATA-4R-Model No. QW-99, India makes), 2450 MHz Frequency, with power output of 140-700 W. The progress of reaction was monitored by TLC (Thin Layer Chromatography).

B. General procedure for synthesis of tetrahydrobenzo[b]pyrans

A mixture of malononitrile (1mmol), aromatic aldehyde (1mmol), dimedone (1mmol), ethanol and L-Tyrosine (15mol %), **(Scheme 1)**was added in a caped 10mL microwave vessel and kept in irradiation cavity. The mixture was irradiated with microwaves at the power of 140W. The total period of microwave irradiation was 1-3 min (Table 2). The progress of reaction was monitored by TLC (ethyl acetate: hexane 4:1). After completion of reaction, the reaction mixture was cooled to room temperature and poured on 10 ml ice water. The separated solid was filtered and washed with water. The residue was dried and recrystallized from ethanol to get the corresponding tetrahydrobenzo[b]pyrans. The products were confirmed by comparisons with authentic samples, IR, ^{1}H NMR, mass spectra and melting points.



Scheme 1

III. RESULT AND DISCUSSION

In a preliminarily investigation onthe model reaction of 4-chlorobenzaldehyde, dimedoneandmalononitrile (entry 4, Table 3), it was found that the reaction could be finished in the presence of catalytic amount of L-Tyrosine under microwave conditions which gave the desired product in good yield. In order to optimize the amount of catalyst, modelreaction was carried out with different amounts of catalyst. With 1 mmol of each reactant, reaction with 5, 10, 15, and 20 mol% of catalyst was tried and it was found that 15 mol% of catalyst is sufficient to get the product in good yield (Table 1). No significant increase in yield was observed with increase in the amount of catalyst. Thus, 15 mol% of catalyst was chosen as optimum amount to catalyze the reaction.In order to optimize the solvent, model reaction was carried out in various solvents and the excellent yield found when ethanol used as solvent Table 2.

Table 1. Optimization of catalyst amount

Entry	Amount of catalyst (mol%)	Time	Yield%
1	-----	30 min	35
2	5	20 min	60
3	10	10 min	92
4	15	2min	92
5	20	2 min	90

Table 2. Optimization of solvent

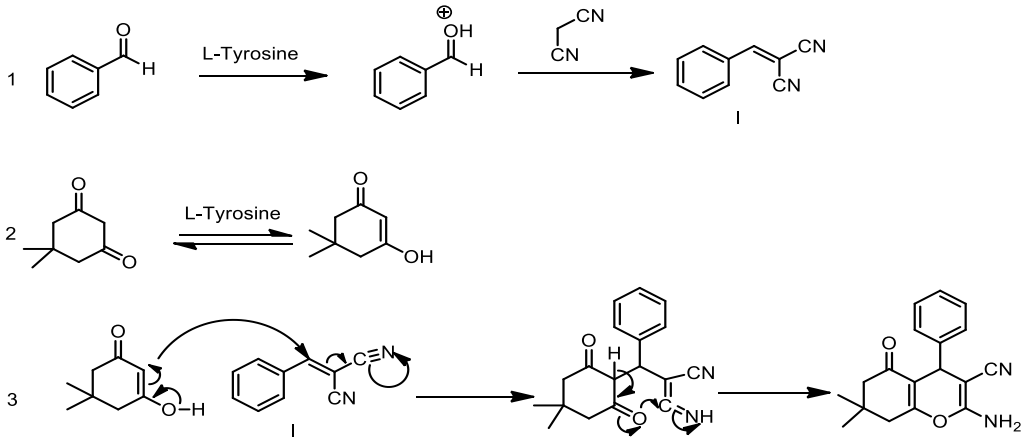
Entry	Solvent	Time	Yield %
1	DMF	30 min	55
2	Acetonitrile	30 min	50
3	Water	30 min	65
4	Methanol	10 min	75
5	Ethanol	2 min	92

After optimization of the reaction conditions, to explore theefficiency and the scope of presented protocol,dimedone (1mmol) and malononitrile (1 mmol) were treated with structurally diverse aromatic aldehydes in the presence of L-Tyrosine as catalyst.The corresponding results are summarized in Table 3. As Table 3 indicates, all aldehydes(including benzaldehyde and arylaldehydes bearing halogens, electron-withdrawing substituents) were successfully reacted to produce the corresponding chromenederivatives in good to excellent yields and in relatively short reaction times. The presented method was successfully used for arylaldehydes with various groupsat different positions such as halides, nitro and hydroxyl.

Table 3. One-pot synthesis of tetrahydrobenzo[b]pyrans catalyzed by L-Tyrosine

Entry	Aldehyde R	Time (min)	Yield%	Melting Point°C	
				Found	reported
1	H	3.5	88	226-228	230-235[13]
2	4-NO_2	1.5	94	147-149	150-153[13]
3	3-NO_2	2	93	210-212	206-208[13]
4	4-Cl	2	92	203-205	225[11]
5	4-OH	2.8	90	216-218	226-228[11]
6	3-OH	3.2	90	235-237	230-232[13]
7	4-Br	2.2	91	218-220	213-215[13]
8	4-F	2	93	236-238	235-237[14]
9	4-OMe	4	92	202-204	201-203[14]
10	3,4-diOMe	4.2	88	164-166	158-160[13]
11	4-Me	3.6	85	210-212	215[13]
12	4-OH, 3-OMe	4.2	86	225-227	230-232[13]
13	Thiophene	3	84	211-213	216-218[13]
14	2-Cl	2.5	88	217-219	215-217[13]
15	2-NO_2	3.3	87	180-182	185-187[13]

4.1.4a. Mechanism



Scheme 17

Spectral data

1. **2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile (Table 3, entry 2).**

Melting point: 247-249^{0}C. IR (KBr) cm^{-1}: 3476 and 3229 (NH_2), 3117 (C-H), 2196 (CN), 1690 (C=O), 1650(C=C),1594, 1516, 1492, 1352. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.12 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 6.94 (s, 2H, NH_2), 4.35 (s, 1H, CH), 2.19-2.50 (m, 4H, 2CH_2), 1.09 (s, 3H, CH_3), 0.96 (s, 3H, CH_3).

2. **2-amino-5,6,7,8-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile (Table 3, entry 12).**

Melting point: 225-227^{0}C. IR (KBr) cm^{-1}: 3474 and 3223 (NH_2), 3118 (C-H), 2195 (CN), 1695 (C=O), 1651(C=C). ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 8.64 (s, 1H, OH), 6.6 (m, 4H, ArH, NH), 6.5 (s, 1H, NH), 4.09 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 2.0-2.5 (m, 4H, 2CH_2), 1.09 (s, 3H, CH_3), 0.98 (s, 3H, CH_3).

IV. CONCLUSION

We reported an atom-economical multicomponent reaction, using energy-efficient microwave irradiation; L-Tyrosine as mild, cost effective and 'greener' catalyst along with eco-friendly green solvent ethanol for the synthesis of tetrahydrobenzopyran. The attractive features of this protocol are the mild reaction conditions, high conversions, operational simplicity and inexpensive and ready availability of the catalyst; which makes it a useful and attractive strategy for the preparation oftetrahydrobenzopyran.

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