Iranian Journal of Catalysis 6(2), 2016, 189-192

IRANIAN JOURNAL OF CATALYSIS

Ammonium chloride catalyzed microwave-assisted synthesis of tetrahydrobenzo[b]pyrans

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Received 31 May 2015; received in revised form 25 December 2015; accepted 30 December 2015

ABSTRACT

In the present work, we have developed a mild, efficient, and environmentally benign method for the synthesis of tetrahydrobenzo[b]pyran derivatives via a three-component cyclocondensation of aldehydes, malononitrile and dimedone utilizing ammonium chloride as a simple, easily available and cost effective catalyst under microwave irradiation. This method has several attracting features such as simple experimental set up, easy work-up procedure, high conversions and short reaction times affording the products in moderate to excellent yield.

***Keywords**: Tetrahydrobenzo[b]pyrans, Ammonium chloride, MW irradiation.*

1. Introduction

Recently, tetrahydrobenzo[b]pyrans have attracted the attention of scientific community as they are widely used as anti-coagulant, diuretic, spasmolytic, anticancer, anti-anaphylactin agents and cognitive enhancers for the treatment of neurodegenerative diseases such as Alzheimer's disease, amyoprophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [1].

Literature survey shows the use of various catalysts for the synthesis of tetrahydrobenzo[b]pyrans such as fructose [2], hexadecyldimethylbenzyl ammonium bromide [3], phthalimide-N-oxyl(POPINO) [4], tetra-methyl ammonium hydroxide [5], palladium nanoparticles [6] etc. Although each method has its own advantages and disadvantages, researchers are more concerned with the development of environmentally benign reactions which will eliminate the utilization of harmful catalysts and reagents with the minimization of toxic waste and byproducts. During the past decade, MW irradiation has emerged as an effective tool in organic synthesis due to short reaction time, uniform and selective heating, higher yields, clean reaction profile and easy work up.

In recent years, ammonium chloride has become a popular catalyst, owing to its greater selectivity under mild reaction conditions, cost effectiveness and eco-friendly nature. Ammonium chloride was effectively used as a catalyst for the synthesis of di(indolyl)methanes [7], spirochromenes and spiroacridines [8] and synthesis of 3,4-dihydropyrimidinones under solvent-free conditions [9]. Recently, Teimouri et al. synthesized α, α' bis(substituted benzylidene) cycloalkanones using ammonium chloride in ethanol under refluxing conditions within 3.5 to 5 hrs [10].

Herein we report a simple, mild and efficient method for the synthesis of tetrahydrobenzo[b]pyrans using ammonium chloride as a catalyst under microwave irradiations (Scheme 1).

2. Experimental

2.1. Materials

Chemical reagents were purchased from SD Fine Chemical Company in high purity. All the materials were AR grade.

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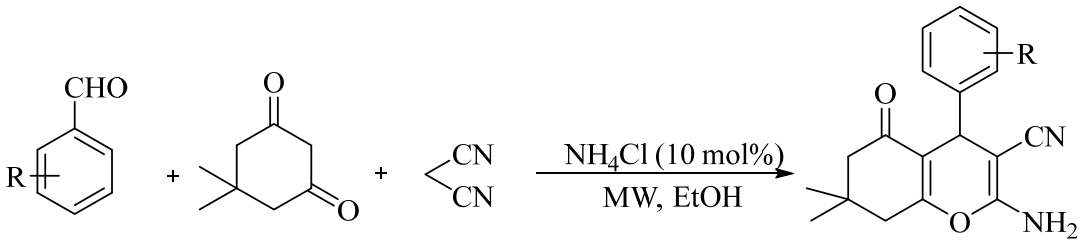


Scheme 1.

2.2. Apparatus

Melting points were determined in open capillaries using a digital melting point apparatus (Optics technology). Infrared (IR) spectra in KBr were recorded using a Perkin-Elmer spectrum 65 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 400 MHz FT-NMR spectrometer in DMSO-d_6 as the solvent and chemical shift values were 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 progresses of the reactions were monitored by TLC (Thin Layer Chromatography).

2.3. General procedure for the synthesis of tetrahydrobenzo[b]pyrans using ammonium chloride under mw irradiations

A mixture of malononitrile (1 mmol), aromatic aldehyde (1 mmol), dimedone (1 mmol), ethanol (2 mL) and ammonium chloride (10 mol %) was prepared properly with the help of glass rod and exposed in a microwave oven at the power of 140W and irradiated for a period of 10 sec at a time. After each irradiation, the reaction mixture was removed from the microwave oven for shaking. The total period of microwave irradiation was 0.5-2 min (Table 2). The progress of reaction was monitored by TLC ethyl acetate: hexane (1:4). 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 comparison with authentic samples, IR, ^{1}HNMR and melting points.

Selected spectral data

*2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (**Entry 2, Table 2**):*

^{1}HNMR (300 MHz, DMSO-d_6): δ= 0.93 (s, 3H), 1.02 (s, 3H), 2.10 (d, *J* = 16.1 Hz, 1H), 2.21 (d, *J* = 16.1 Hz, 1H), 2.50 (s, 2H), 4.19 (s, 1H), 7.05 (s, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H) ppm. IR (KBr): $\bar{\nu}$= 3381, 3184, 2959, 2188, 1674, 1635, 1604, 1365, 1216 cm^{-1}.

*2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile (**Entry 5, Table 2**):*

^{1}HNMR (300 MHz, DMSO-d_6): δ= 0.94 (s, 3H), 1.02 (s, 3H), 2.07 (d, *J* = 16.07 Hz, 1H), 2.21 (d, *J* = 16.03 Hz, 1H), 2.52 (s, 2H), 4.35 (s, 1H), 7.17 (s, 2H), 7.44 (d, *J* = 8.35 Hz, 2H), 8.14 (d, *J* = 8.35 Hz, 2H) ppm. IR (KBr): $\bar{\nu}$ = 3407, 3317, 3176, 2183, 1671, 1630, 1594, 1521, 1350, 1216, 1031 cm^{-1}.

3. Results and discussion

Synthesis of tetrahydrobenzo[b]pyran was carried by using p-chlorobenzaldehyde as a sample reaction in different reaction conditions as mentioned in Table 1, in an order to optimize the reaction conditions, that is, solvents, temperature and other reaction conditions.

Table 1: Optimization of reaction conditions.

Entry	Catalyst	Reaction conditions	Time (min)	Yield (%)
1	No catalyst	EtOH, RT, stirring	30	No product
2	No catalyst	EtOH, MW, 140 Watt	8	85
3	NH_4Cl	EtOH, MW, 140 Watt	0.5	95

Table 2: Synthesis of tetrahydrobenzo[b]pyrans using NH_4Cl as catalyst under microwave irradiations.

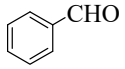
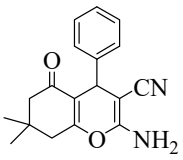
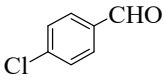
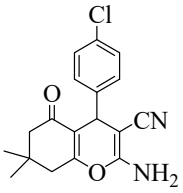
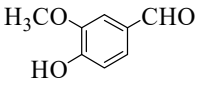
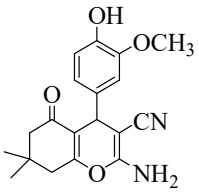
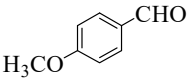
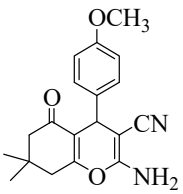
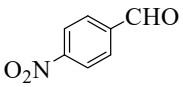
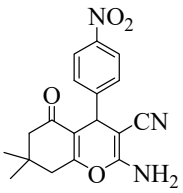
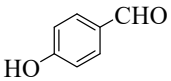
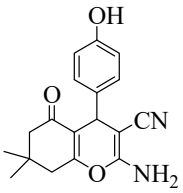
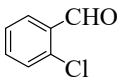
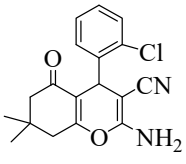
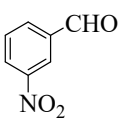
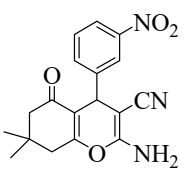
Entry	Aldehyde	Product	Time (sec)	Yield (%)	m.p. (°C)		Ref.
					Found	Reported	
1			120	85	230-232	234-235	[11]
2			30	95	213-214	215-217	[12]
3			120	88	236-238	238-240	[13]
4			120	84	198-199	201-202	[11]
5			60	90	178-179	179-180	[14]
6			60	88	228-229	224-226	[11]
7			60	92	217-218	214-215	[15]
8			60	84	212-213	214-216	[12]

Table 3. Comparison of microwave assisted, ammonium chloride catalyzed synthesis of tetrahydrobenzo[b]pyran with some literature methods.

Entry	Catalyst	Conditions	Time	Yield (%)	Ref.
1	PDBSA[a]	H_2O, Reflux	4-7 h	69-90	[1]
2	TBAB	H_2O, Reflux	30- 45 min	89-95	[16]
3	Imidazole	H_2O, 80°C	30 min	85-95	[17]
4	Starch	Starch , 50°C	30-75 min	82-94	[18]
5	NH_4Cl	MW, 140 W	30 sec - 2 min	85-95%	This work

[a]PDBSA = p-dodecylbenzene sulfonic acid.

From Table 1, when the reaction was carried under catalyst free conditions at room temperature, no product formation was observed after 30 minutes. Under microwave irradiation and catalyst free conditions, the reaction was completed within 8 min affording the corresponding product in 85% yield. However, the use of ammonium chloride and microwave irradiation significantly reduced the reaction time to 0.5 minutes and also increased yield of the corresponding product. Thus, it is clear that the reaction using NH_4Cl under microwave irradiation is better with excellent yield of the products. To check generality and scope of this newly developed synthetic protocol, we performed this reaction on various substituted aromatic aldehydes (Table 2). It was found that 4-chlorobenzaldehyde, 4-hydroxybenzaldehyde and 4-nitrobenzaldehyde afforded the products in shorter time as compared to the rest of aldehydes. The nature of substituent played no significant role on the time and yield of the corresponding products. All the products were obtained in excellent yield within a short reaction time. The advantages and superiority of the present method for the synthesis of tetrahydrobenzo[b]pyrans are highlighted in Table 3 by comparing the results with some of the literature protocols. Use of ethanol as a green reaction medium, application of microwave irradiation and short reaction time make the present method highly useful for the synthesis of tetrahydrobenzo[b]pyrans.

4. Conclusions

In summary, we have developed a mild, efficient, environmentally benign method for the synthesis of pharmaceutically valued tetrahydrobenzo[b]pyran derivatives utilizing ammonium chloride catalyst under microwave irradiation in excellent yield. The present protocol has attractive features like a cleaner reaction profile, simple experimental and work-up procedures, high conversions, shorter reaction time affording the products in excellent yield, hence, it places itself higher to be superior over many existing synthetic methods.

Acknowledgments

Authors are thankful to the principal, Dr. M. L. Jadhav, Deogiri College, Aurangabad for providing laboratory facilities.

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