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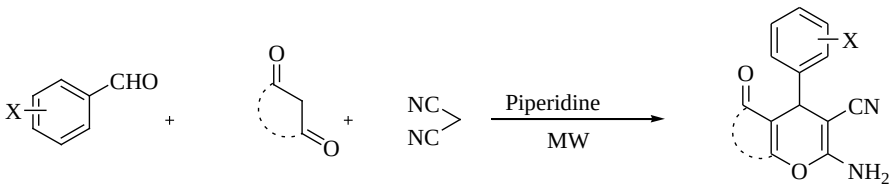
Base Catalyzed one pot green synthesis of Tetrahydrobenzo[b]pyran

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Graphical abstract:

Base catalyzed green protocol has been developed for one-pot three-component condensation of aldehydes, malononitrile and diketo compounds for the synthesis of biologically important moiety tetrahydrobenzo[b]pyran derivatives. The reaction affords moderate to excellent yield of products. Benzopyrans are basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins. These compounds are also industrially important as cosmetics, pigments and potentially biodegradable agrochemicals.



Piperidine catalyseded synthesis of tetrahydrobenzo[b]pyrans

Key words:Tetrahydrobenzo[b]pyran, piperidine, microwave

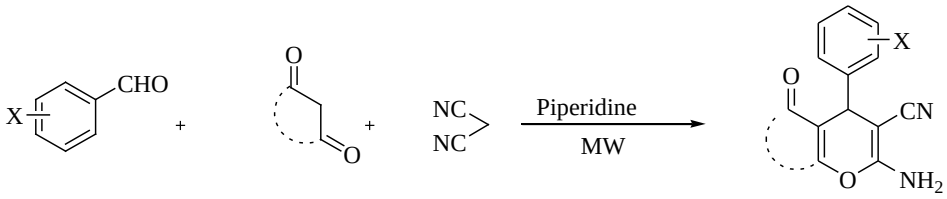
Introduction:

Tetrahydrobenzo[b]pyrans has attracted attention of researchers in the field of drug discovery [1]due to their wide applications. These compounds are found active against microorganisms and reported as spasmolytic, anti-coagulant, diuretics agents anticancer, anti-anaphylactic and [2]. They worked as cognitive enhancers in the treatment of neurodegenerative Alzheimer's disease, in Parkinson's disease,in amyotrophic lateral sclerosis, in AIDS associated dementia and Down's

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syndrome.They are also used for the treatment of schizophrenia and myoclonus, Huntington's disease [3] etc. tetrahydrobenzo[b]pyran nucleus are found in structural scaffold of several natural products [4].They are found to be converted into pharmacologically important calcium antagonist dihydropyridine systems [5]. Along with their biological importance, some 2-amino-4H-pyrans have been widely used as photoactive materials.

Witnessing the wide applications of tetrahydrobenzo[b]pyran,their synthesis received great importance in medicinal chemistry and organic synthesis. Several methods for the synthesis of tetrahydrobenzo[b]pyran derivatives have been reported, varied from one-pot to multi-step approaches [6]. Among various strategies of synthesis, most popular method involve one-pot, three-component condensation of malononitrile, aldehyde and dimedone in various reaction conditions using various catalysts such as TBAB,NaBr, Na_2SeO_4 , Starch,hexadecyldimethylbenzyl ammonium bromide, p-dodecylbenzenesulfonic acid KF-alumina,tetra-methyl ammonium hydroxide, Imidazole,and etc. these reported methods have certain advantages and disadvantages. In present work the catalytic activity of piperidine for the synthesis of tetrahydrobenzo[b]pyran derivatives under microwave irradiation has been studied.



Piperidine catalyseded synthesis of tetrahydrobenzo[b]pyrans

Experimental:

All chemicals required for synthesis were purchased from Spectrochem or SD fine chemicals and used without purification. Reaction progress was monitored by Thin Layer Chromatography (TLC). Synthesized products were confirmed by comparing TLC of products prepared by reported methods. Products were further confirmed by taking melting point of

products in capillaries open at one end. IR spectra of products were taken by preparing KBR discs and product were scanned on Perkin Elmer FT-IR spectrometer.

General procedure for the synthesis of tetrahydrobenzo[b]pyrans:

Aromatic aldehyde (1mmol), diketo compound (1mmol), malononitrile (1mmol), piperidine (1 mL) and ethanol (1 mL) was mixed using a glass rod and the mixture was irradiated in microwave oven at 210 watts periodically after 10 sec each. The reaction progress was monitored by TLC in ethyl acetate: hexane (1:4). After completion of reaction, mixture was cooled to room temperature and poured on 5 ml ice. The solid product formed was filtered and washed with water. The residue obtained was dried and recrystallized using ethanol to afford corresponding tetrahydrobenzo[b]pyrans. The products were confirmed by comparisons with prerecorded samples, melting points, IR and ^{1}H NMR.

Spectral data for new derivatives of tetrahydrobenzo[b]pyrans

2-Amino-3-cyano-5, 6, 7, 8-tetrahydro-7, 7-dimethyl-4-(3, 4-dimethoxyphenyl)-5-oxo-4H-benzopyran: mp: 164-166 ^{o}C. IR (KBr) cm^{-1} 3404 (NH_2), 2192 (CN), 2955 (C-H), 1679 (C=O), 1603 (C=C)1656 (C=C).^{1}H NMR (DMSO-d_6), 6.69-6.70 (d, 1H, Ar-H), δ 6.86-6.88 (d, 1H, Ar-H), 6.64-6.67 (dd, 1H, Ar-H), 6.94 (s, 2H, NH_2), 3.72 (d, 6H, $(OCH_3)_2$), 4.13 (s, 1H), 2.13(d, 1H, H), 2.50 (s, 2H), 2.09 (d, 1H), 0.99 (s, 3H, CH_3), 1. 06 (s, 3H, CH_3).

5-Acetyl-2-amino-6-methyl-4-(3-nitrophenyl)-4H-pyran-3-carbonitrile: mp: 182-183 ^{o}C. IR (KBr) cm^{-1}3392 (NH_2), 2297 (C-H), 2189 (CN), 1674 (C=O), 1640 (C=C), 1603 (C=C). ^{1}H NMR (DMSO-d_6), 8.01(1H, Ar-H), 7.62 (2H, Ar-H), 6.80 (2H, s, NH_2), 4.64 (1H, s, –CH), 2.33 (3H, s, –CO–CH_3, acetyl), 2.1 (3H, s, –CH_3).

Results and discussion:

Initially a reaction was checked by using 4-chlorobenzaldehyde at different reaction conditions and results obtained are mentioned in Table 1.

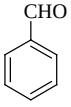
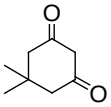
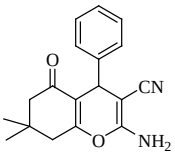
Table 1:Reaction at different reaction conditions

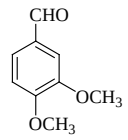
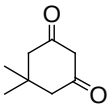
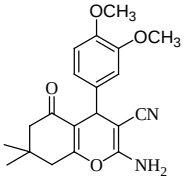
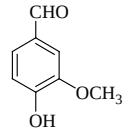
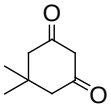
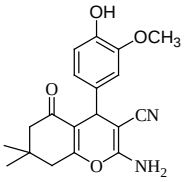
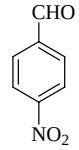
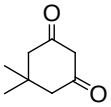
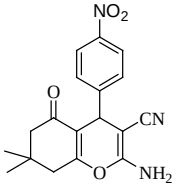
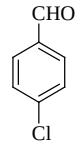
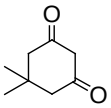
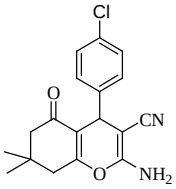
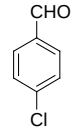
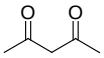
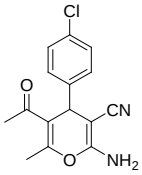
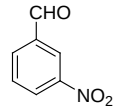
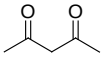
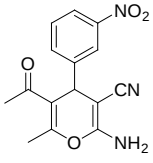
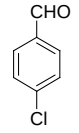
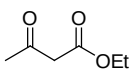
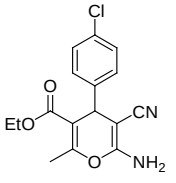
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Entry	Catalyst	Reaction conditions	Time	Yield (%)
1	Without catalyst, Without solvent	RT, stirring	30 min	No reaction
2	No catalyst	CH_3CH_2OH, mw, 210 watts	8 min	80
3	Piperidine	CH_3CH_2OH, mw, 140 watts	90 sec	92

The reaction without catalyst and solvent was carried out which did not show any progress till 30 min. The reaction if carried out in the absence of catalyst using microwave irradiation as energy source, was completed within 8 to 10 mins. When piperidine was used as catalyst and ethanol as solvent along with microwave irradiation, the reaction was completed just within 90 seconds.The reaction is characterized by faster reaction time and excellent yield of products. Under these optimized conditions, piperidine was found to worked very efficiently as catalyst in ethanol solvent. Benzaldehyde containing electron withdrawing substituents shows short reaction times compared to other aldehydes which do not contain any electron withdrawing substituent. The products obtained shows excellent yield and shorter reaction time (Table 2).

Table 2:Microwave assisted, piperidine 257atalyzed synthesis of tetrahydrobenzo[b]pyrans

Entry	Aldehydes	1,3-Dicarbonyl	Products	Time (sec)	Yield @ (%)	M. P. (°C) Observed
1.				120	86	226-227

2.				150	82	165-167
3.				150	86	226-228
4.				100	88	249-250
5.				90	90	205-206
6.				120	84	172-174
7.				140	80	183-184
8.				130	84	171-173

Conclusion:

In summary, we have carried out piperidine catalyzedenergy efficient synthesis of biologically important tetrahydrobenzo[b]pyran derivatives by using microwave irradiation with excellent yield of product. This protocol has salient features such as clean reaction profiles, simple and easy experimental and work-up procedures, high conversions and shorter reaction time; hence advantageous over many existing synthetic strategies.

Acknowledgment

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