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Microwave Assisted Synthesis and Biological Screening of Dihydro pyrimidine Derivatives Using DABCO: An Efficient Catalyst

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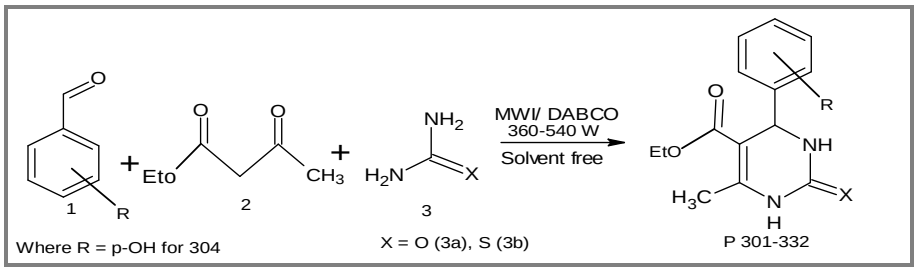
ABSTRACT

The simple and green synthetic method proposed for the synthesis of biologically active multi functional dihydropyrimidin-2-(1H)-one/thione derivatives of series (5-phenyl-5,8-dihydropyrimido [4,5-d]pyrimidine-2,4,7(1H,3H, 6H) -trione) by the use of highly efficient DABCO as Catalyst under microwave assisted method . The multicomponent condensation of three carried out with the yield of new derivatives in high yield within desired time period. The catalyst can be reused and recovered easily at mild reaction condition and MWI technique always guarantees desired results with eco-friendly output. Further, the structural features of newly synthesized compounds were confirmed by their characterized by IR, ^{1}HNMR, ^{13}CNMR, Mass spectroscopic techniques and their biological screening were done activities against gram +ve bacteria and gram –ve bacteria and anti-fungal activities using cup-plate diffusion method.

Graphical Abstract

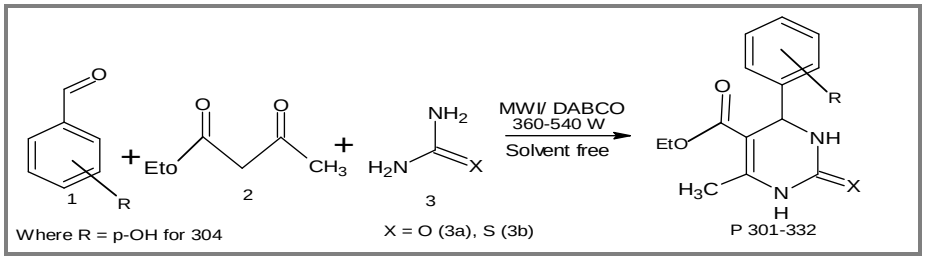


Biginelli Reaction(SP_1-SP_{28})

Keywords: Dihydropyriminies, Biginelli reaction, DABCO Catalyst, Microwave Assisted method, Anti-microbial activities.

INTRODUCTION

Dihydropyrimidinones or pyrimidinones are multi-functionalized nitrogen bearing heterocyclic compounds initially formed by multicomponent one-pot condensation reaction of variable aldehydes, beta-ketoesters, and urea/thiourea first reported by P. Biginelli [**1**].These compounds have gained much importance due to their wide spectrum of biological and pharmaceutical properties [**2-6**]. Due to their innumerous biological, industrial and pharmaceutical applications have attracted the attention of researchers and chemists to design and development of a wide range of synthetic methodologies for these novel drugs. Their dominant presence in DNA and RNA as bases is of great importance in living world and become very important in the world of synthetic organic domain. To synthesize highly valuable and life saving heterocyclic drugs, innumerous catalysts and solvents have been used. In recent years several methods and techniques for the synthesis of dihydropyrimidines and its derivatives have been developed to improve and modify this reaction promoted by Lewis acids such as $In(OTf)_3$ [**7**], $TaBr_5$ [**8**] , EPZ-10 [**9**], Ph_3P-C_2Cl_6 [**10**], DABCO/H_2O [**11**], $Bi(NO_3)$ [**12**], CaF_2 [**13**], large number of ionic liquids used [**14, 15**]and some other catalysts supported by some natural, nontoxic materials were also employed such as KF-montomorillonite [**16**] as well as Red Sea Sand [**17**]. These improved methods which are reported earlier still suffers from many major drawbacks such as use of acidic catalysts, use of bulky and toxic solvents, vigorous reaction condition and environment affecting working setup. Even many new green and advanced techniques such as microwave irradiation, ultrasound irradiation [**18, 19**] have been successfully used, some of the above protocols still suffer by one or another way. Therefore, to overcome all these drawbacks, we have proposed a newer microwave assisted synthetic method for the derivatives, accompanied with higher yields by using diazobicyclooctane(DABCO), a green and efficient catalyst under solvent free conditions (Scheme 1).



Scheme 1. Biginelli Reaction(SP_1-SP_{28})

MATERIALS AND METHODS

Material: All chemicals were AR grade. Analytical thin layer chromatography was carried out on Merck precoated silica gel 60 F_{254} plates (thickness 0.25 mm). Spots were visualized with UV light and Iodine vapours. Column chromatography was carried out using silica gel (60-120 mesh). Melting points were determined in open capillary and are uncorrected. Products obtained were identified by their physical and spectral data. ^{1}H-NMR and ^{13}C-NMR analysis were carried out on a Bruker AM-400 spectrometer in $CDCl_3$/DMSO-d_6. IR spectra were recorded on Bruker IR-Alpha-Eco-ATR spectrophotometer. Mass spectra were recorded on Bruker (EIMS) mass spectrophotometer. Domestic microwave was taken for heating purposes. Elemental analysis of the compounds was carried out on ElementarVario EL III Carlo Erba 1108 model at SAIF-CDRI, Jammu J&K.

General Procedure

Method for Synthesis of dihydropyrimidine by DABCO catalyst: An equimolar mixture of substituted aromatic aldehydes 1 (10 mmol), ethyl acetoacetate 2 (10 mmol) and urea/thiourea 3a/b (10 mmol) and DABCO as a catalyst (2 mmol) taken in 50 mL microwave flask were irradiated in unmodified domestic microwave at 340-560 W for 3-10 min under solvent free condition. The

reaction was monitored by thin layer chromatography using silica gel-G plates. Ethyl acetate and n-hexane mixture was used as eluting solvent. After drying of plates in air, spots were marked and exposed to iodine chamber/UV chamber. Upon the completion of reaction the solid produced was filtered under reduced pressure and recrystallized from 95% ethanol. (Scheme 1)

RESULTS AND DISCUSSION

This method offers a best and alternative route for the synthesis of 3,4 dihydropyrimidines (SP_1-SP_{28}) derivatives with excellent yields 80-97% in least reaction times. To explore the versatility of catalyst used and novelty of method applied. We investigated the effect of the catalyst used in basic reaction setup. It was observed that the catalyst played a crucial role in terms of the yields obtained within 5 min promoted by microwave radiation. The reaction was carried out by reacting of p-hydroxy benzaldehyde, ethyl acetoacetate/cyclohexadione and urea/thiurea in a suitable mole ratio under microwave oven for 5 min, on regular heating of mixture at an interval of 1 min till reaction completion and the corresponding product was formed. Using simple and direct workup, the expected derivatives were isolated in excellent yields compared to results obtained without using these conditions. The effect of the catalyst amount on these reactions is shown in table 1. By increasing the amount of the catalyst, higher yields were obtained. From table 1, we found that on changing the conc. of catalyst results drastic changes, increasing the amount of catalyst product yield increases till it reaches a constant level at 50 mg (where yield were best 97%), on further increase of catalyst yield does not show any notable change. This confirms that 50 mg amount of catalyst serves best for these reactions to get resulting derivatives of dihydropyrimidines (SP_1-SP_{28}) in high yield.

Table1. Effect of various amount of DABCO catalyst on dihydropyrimidines synthesis

Entry	Amount of DABCO	Yield %
1	No catalyst	89
2	10 mg	90
3	20 mg	92
4	30 mg	94
5	40 mg	95
6	50 mg	97
7	100 mg	96

In the proposed work, microwave assisted tool is introduced which worked effectively and promoted rate of reaction by reducing the time drastically from hours to minutes and resulted in high yields of pure products shown in tables 2. Hence it served as an efficient and green tool for the synthesis of targeted and novel derivatives by eliminating almost all drawbacks associated with this reaction reported earlier.

Table 2. Comparison of the results using different catalysts

Entry	Catalyst	Reaction Time (h)	Yield %
1	DABCO/H_2O	2.00	89 [20]
2	Ionic liquid [bmim]Br	0.55	93 [21]
3	$SbCl_3/SiO_2$	1.10	90 [22]
4	EPZ-10	0.45	91 [23]
5	[Btto][p-TSA]	0.40	92 [24]
6	DABCO	0.03	97 Present Work

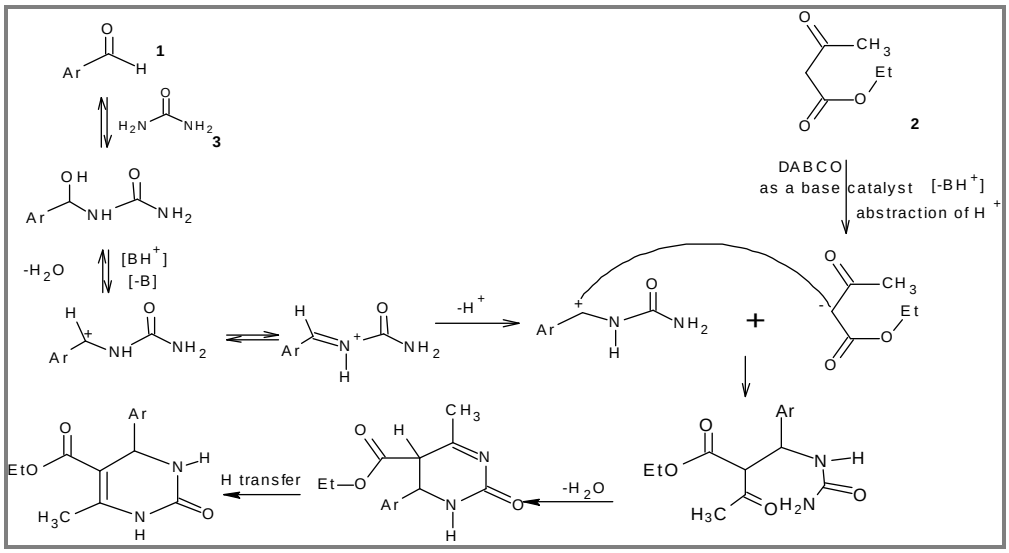
To investigate the advantage, generality and versatility of the DABCO catalyst, a comparative study has been done of this catalyst with other catalysts such as DABCO/H_2O, Ionic liquid-[bmim]Br, $SbCl_3/SiO_2$, EPZ-10, [Btto][p-TSA] which are recently reported. DABCO in present work shows

relatively more efficient catalytic activity in terms of reaction times and yields of the obtained products in presence of microwave irradiation shown in table 2.

The effect of variety of substituted aldehydes was examined by using reaction of substituted aryl aldehydes, 1 ethyl acetoacetate 2a and urea/thiourea 3a/b under given conditions and the results are given in table 3. In general, the heteroaryl aldehydes carrying electron donating groups reacted effectively and gave the product as 3,4-dihydropyrimidines in good to excellent yields in lesser time duration (Scheme 2).

Table 3. Physical data of all synthesized compounds (SP_1-SP_{28})

Product	Ar-R	X	Time (min)	Yield (%)
SP_1	Ar-H	O	4	89
SP_2	Ar-2-Cl	O	5	92
SP_3	Ar-4-OH	O	4	91
SP_4	Ar-2,4-OCH_3	O	5	92
SP_5	Ar-4-CH_3	O	4	94
SP_6	Ar-2-OCH_3	O	5	95
SP_7	Ar-2-OH	O	3	88
SP_8	Ar-2-C_6H_5	O	6	83
SP_9	Ar-4-OCH_3	O	3	97
SP_{10}	Ar-4,6-CH_3, 2,3-OH	O	5	88
SP_{11}	Ar-2,4-NO_2	O	5	92
SP_{12}	Ar-4-$N(CH_3)_2$	O	6	83
SP_{13}	Ar-4-NO_2	O	5	93
SP_{14}	Ar-4-OH, 3-OCH_3	O	4	94
SP_{15}	Ar-H	S	5	86
SP_{16}	Ar-2-Cl	S	5	87
SP_{17}	Ar-4-OH	S	4	87
SP_{18}	Ar-2,4-OCH_3	S	5	92
SP_{19}	Ar-4-CH_3	S	4	93
SP_{20}	Ar-2-OCH_3	S	3	94
SP_{21}	Ar-2-OH	S	4	87
SP_{22}	Ar-2-C_6H_5	S	6	84
SP_{23}	Ar-4-OCH_3	S	4	96
SP_{24}	Ar-4,6-CH_3, 2,3-OH	S	4	89
SP_{25}	Ar-2,4-NO_2	S	3	90
SP_{26}	Ar-4-$N(CH_3)_2$	S	6	84
SP_{27}	Ar-4-NO2	S	6	91
SP_{28}	Ar-4-OH, 3-OCH_3	S	4	90



Scheme 2. Proposed mechanism for dihydropyrimidines.

The synthetic pathway followed by this synthetic route to prepare derivatives ranging from (SP_1-SP_{28}) involves two step as usual found in other earlier discussed cases, the mechanism follows the Knoevenagel addition of heteroaryl aldehyde 1 and urea/thiourea (3a/b) resulting cation intermediate, followed by Michael addition of ethyl acetoacetate/cyclohexadione (2a/2b) gives adduct which on tautomerization (proton transfer) and heterocyclization gives polyfunctionalized 3,4-dihydro pyrimidine derivatives (SP_1-SP_{28}) with the release of two molecules of water, in presence of catalytic amount of DABCO under microwave irradiation.

Further confirmation of all synthesized products is done by their structures analysis with the help of their elemental analysis, M.P and spectroscopic techniques like ^{1}H NMR, ^{13}C NMR, Mass spectra and IR and their biological activities were screened against microbes (bacteria and fungi) to know bio-activeness of these compounds and results obtained reveals that they are effectively active.

APPLICATION

Biological Screening

Antibacterial and Antifungal activity: The results of selectively tested compounds of dihydro pyrimidine and poly fused hexahydroquinazoline are presented in (Table 4), indicate that all selected compounds pertains antimicrobial activity against four bacteria and two fungi taken for study.

Antibacterial activity against four bacteria; the compounds SP_1 and SP_{15} have shown poor activity, compounds SP_{18} and P_{22} exhibit moderate activity while as SP_3, SP_7, SP_{11} and SP_{24} exhibit highest activity against *E. coli;* similarly, the compoundSP_1have shown poor activity, compounds SP_{15}, SP_{22} and SP_{24} exhibited moderate activity and SP_3, SP_7, SP_{11} and SP_{18} exhibited highest activity against *S.typhi;* similarly, the compounds SP_{11} and SP_{22} have shown poor activity, compounds SP_1 and SP_{11} exhibited moderate activity and SP_3, SP_7, SP_{18} and SP_{24} exhibited highest activity against *S. aureus;* similarly, theSP_1 and SP_{18} have shown pertain poor activity, while as SP_3, SP_7, SP_{11}, SP_{15} and SP_{24} exhibit highest activity against *B.subtilis.*

Concerning the antifungal activities; the compounds SP_1 and SP_{28} exhibit poor activity while as compounds SP_{15} and SP_{24} exhibited moderate activity and SP_3, SP_7, SP_{11}, SP_{18} and SP_{22} exhibited highest activity against *C. albicans;* similarly, the compounds SP_1 and SP_{15} exhibit poor activity while as compounds SP_{18} and SP_{22} exhibited moderate activity and SP_3, SP_7, SP_{11} and SP_{24} exhibited highest activity against *A.niger.*

Table 4 Antimicrobial activity of dihydropyrimidines*in vitro*

Entry	Zone of inhibition in mm (Antibacterial activity)				Zone of inhibition in mm (Antifungal activity)	
Comp.	*E. coli*	*S. typhi*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
SP_1	10	6	16	11	8	10
SP_3	18	17	19	18	18	17
SP_7	19	21	18	20	17	19
SP_{11}	18	17	16	18	17	18
SP_{15}	9	16	7	17	16	13
SP_{18}	16	17	18	14	17	16
SP_{22}	15	16	13	17	17	15
SP_{24}	17	16	18	17	16	18
	Ciprofloxacin				Amphotericin B	
	24	25	26	24	26	25

CONCLUSION

The highly efficient and green synthetic protocol have been developed by the involvement of eco-friendly and simple Microwave irradiation technique, in presence of green catalyst diazobicyclooctane (DABCO) to synthesis biologically active multifunctional dihydropyrimidin-2-(1H)-one/thione

derivatives in the range of SP_1-SP_{28} with highest yield in limited framed time duration. Different spectral techniques such IR, ^{1}HNMR, ^{13}CNMR and Mass spectroscopic techniques confirmed the newly prepared derivatives and further their biological screening have been successfully carried out with positive results.

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