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Research Article

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Microwave Irradiated Convenient Synthesis of 1, 2, 3, 4-Tetrahydropyrimidine-5-Carbonitrile Derivatives

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ABSTRACT

A multicomponent reaction involving one-pot reaction of ethylcyanoacetate, Urea and arylaldehydes in presence of p-TSA, reflux or MWI. Aldehyde (3 mmol), ethyl cyanoacetate or phenyl acetic acid (3 mmol), urea (4.5 mmol) and p-TSA were mixed by stirring in a 25 mL round bottom flask for specified time at a temperature of 70°C, reflux for 7-9 h or MWI with 6-8 mins. (Scheme I). The products were further confirmed by spectral analysis data.

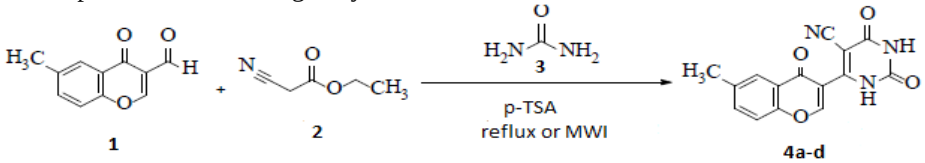
Keywords: One pot synthesis; Tetra hydro pyrimidines; MWI

INTRODUCTION

Tetrahydropyrimidines (THPMs)/Dihydropyrimidines (DHPMs) represent animportant group of highly valuable heterocyclic motifs in the field of medicinalchemistry [1]. Dihydropyrimidines display a wide range of biological activities such ascalcium channel modulators, adrenergic receptor antagonist, mitotic kinesin inhibitor, antiviral, antibacterial [2]. Enastron, monastrol and piperastrol [3] anti-inflammatory [4] and antiviral properties [5].

The examples ofapproved therapeutic agents incorporating tetra- and di-hydropyrimidine molecularframeworks are given in DHPMs are commonly synthesised *via* Biginellireaction and THPMs are usually synthesised *via* Biginelli-like transformation [6-8] oralternatively, using the two-step reaction involving Knoevenagel condensationfollowed by urea annulation [9]. Tetrahydropyrimidine is higher saturated pyrimidine nucleus with two less double bonds. The tetrahydropyrimidines are small, very soluble organic molecules, neutral at physiological PH, which do not hinder with normal cellular functions. They are zwitter ion molecules, and the amidine group of the THPs is positively charged [10].

Medicinal chemistry as a systematic discipline has introduced several new techniques above the final few years in order to speed up the drug discovery process, such as combinatorial chemistry, microwave-assisted organic synthesis and high-throughput purification [11]. The matter is thus the range of new molecules from this huge universe that have the potential to be biologically active [12].



Scheme-I

EXPERIMENTAL SECTION

Melting points were determined on a Cintex melting point apparatus and are uncorrected. Infrared spectra were taken on SHIMADZU-FTIR-8400Spectrophotometer instrument in the frequency range of 4000-400 cm-1 by KBr powder method. The ^{1}H NMR spectra were recorded on a BRUKER Spectrometer (400 MHz). Chemical shifts were reported in parts per million using tetramethylsilane as an internal standard and were given in δ units. The solvent for NMR spectra was $CDCl_3$ and DMSO-d6. All the products were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60F254 (Merck) plates using UV light for detection. Common reagent grade chemicals are either commercially available and were used without further purification.

Aldehyde (3 mmol), ethyl cyanoacetate or phenyl acetic acid (3 mmol), urea (4.5 mmol) and p-TSA were mixed by stirring in a 25 mL round bottom flask for specified time at a temperature of 70°C under reflux for 7-9 h or MWI with 8-11 mins. The reaction mixture was cooledand ethanol was added to solubilize the product. The remaining solid catalyst wasfiltered, washed with ethanol (3 × 15 mL) and ethyl acetate (2 × 10 mL) and reused forfurther catalytic cycles. The filtrate was evaporated under reduced pressure to obtain the product. The crude product was further purified by recrystallization from suitablesolvent (Ethanol or DMSO).

RESULTS AND DISCUSSION

The synthetic approach of substituted 1,2,3,4-tetrahydro-pyrimidine-5-carbonitriles is profiled in Scheme I**.** Reaction time, yield, physical and analytical data and Spectral data of these compounds are given in Table 1**.**

Table 1 : Reaction time and % yield

Compound	Conventional Method		Microwave Method	
	Reaction Time (h)	%Yield	Reaction Time (min)	%Yield
4a	8.5	78	6	94
4b	9	77	7.5	90
4c	10	79	8.5	92
4d	10.5	80	8	90

6-(4-Oxo-4H-[1] Benzopyran-3-yl)-2,4-Dioxo-1,2,3,4-Tetrahydropyrimidine-5-Carbonitrile

4a White solid, M.p. 210-213°C. Anal. Calcd ($C_{14}H_7N_3O_4$): C,59.77 H, 2.51; N, 14.92. Anal. Found : C, 59.75;H, 2.54; N, 14.95. IR (KBr, cm-1):1647 (C=O), 1732(2 × C=O), 2218 (CN), 3262 (NH), 3442 (NH). 1HNMR (400MHz, DMSO-d6): δ 10.86 (s, 1H, NH), 8.18 (s, 1H, NH), 6.67(s, 1H), 7.1-7.9 (m, 4H, Ar-H). 13CNMR (100 MHz, DMSO-d6): δ 179.14, 169.24, 167.52, 161.32, 156.85, 150.27,135.27, 133.23, 127.44, 124.16, 121.51, 113.84, 109.11,91.21. ESI-MS m/z 282.1 (M++1).

6-(6-Methyl-4-Oxo-4H-[1] Benzopyran-3-yl)-2,4-Dioxo-1,2,3,4 Tetrahydropyrimidine-5-Carbonitrile

4b White solid, M.p. 225-229°C. Anal. Calcd ($C_{15}H_9N_3O_4$): C,61.02; H, 3.07; N, 14.23. Anal. Found: C, 61.05;H, 3.03; N, 14.26. IR (KBr, cm-1):1656 (C=O), 1730(2 × C=O), 2225(CN), 3281 (NH), 3444 (NH).1HNMR (400MHz, DMSO-d6): δ 11.20 (s, 1H, NH), 8.74 (s, 1H, NH), 7.37(s, 1H), 7.4-7.8 (m, 3H, Ar-H), 3.36 (s, 3H, CH_3). 13CNMR (100 MHz, DMSO-d6): δ 180.22, 172.94, 168.21,162.44, 158.07, 152.11, 138.76, 133.36, 127.12, 123.34,120.11, 115.81, 107.31, 86.14, 27.04. ESI-MS m/z 296.1 (M++1).

6-(6-Chloro-4-Oxo-4H-[1] Benzopyran-3-yl)-2,4-Dioxotetrahydropyrimidine-5-Carbonitrile

4c White solid, M.p. 220-223°C. Anal. Calcd ($C_{14}H_6C_lN_3O_4$):C, 53.27; H, 1.92; N, 13.31. Anal. Found: C,53.25; H, 1.95; N, 13.27. IR (KBr, cm-1):1694 (C=O), 1738(2 × C=O), 2233 (CN), 3297(NH), 3396 (NH). 1HNMR (400MHz, DMSO-d6): δ 10.86 (s, 1H, NH), 8.25 (s, 1H, NH),7.01(s, 1H), 7.2-7.8 (m, 3H, Ar-H). 13CNMR (100MHz, DMSO-d6): δ 181.02, 171.23, 168.47, 163.72, 154.24, 149.89, 136.76, 135.21, 132.70, 130.49, 124.09, 119.76,113.28, 88.76. ESI-MS m/z 316.2 (M++1).

6-(Indol-3-yl)-2,4-Dioxo-1,2,3,4-Tetrahydropyrimidine-5-Carbonitrile

4d Orange solid, M.p. 203-208°C. Anal. Calcd ($C_{13}H_8N_4O_2$): C,61.90; H, 3.20; N, 22.21. Anal. Found : C, 61.86;H, 3.25; N, 22.23. IR (KBr, cm-1): 1736 (2 × C=O), 2218 (CN),3166 (NH), 3241 (NH), 3389 (NH). 1HNMR (400 MHz, DMSO-d6): δ 11.06 (s, 1H, NH), 9.82 (s, 1H, NH-Indole), 8.31(s, 1H, NH), 8.23 (s, 1H), 7.2-8.0 (m, 4H, Ar-H). 13CNMR (100 MHz, DMSO-d6): δ174.56, 168.24, 154.51,141.09,131.24, 129.82, 127.29, 126.87, 124.17, 121.75, 119.05,115.12, 92.43. ESI-MS m/z 253.2 (M++1).

CONCLUSION

A convenient and highly efficient protocol for the synthesis of 1,2,3,4-tetrahydro-pyrimidine-5-carbonitriles 4a-d in solvent-free conditions under MW irradiation is demonstrated. The significant advantages of this procedure are short reaction times, simple experimental work-up procedure, high yields and excellent purities of the products.

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