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Synthesis & Characterization of Heterocyclic Amide Derivative via Ugi Reaction

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ABSTRACT

Synthesis of heterocyclic amid derivative (*cyclohexanecarbox-amide*) by the reacting four-compound [Formaldehyde], [N-(phenethyl)formamide], [Cyclohexanecarboxylic acid], and [Creatinine] as amine source. This reaction is practical extension of *(Ugi reaction*). The derivatives have been performed with other catalytic agents under temp (-10°C) and the organic synthesis was monitories by TLC [thin layer chromatography] and the formation of final compound proofed by Nuclear Magnetic Resonance Spectra [^{1}HNMR] [^{13}CNMR] BRUKER (500MHz, CDL_3), (125MHz, CDL_3 and Infra-Red spectra [FT-IR] (shimadzu).

Keywords: Ugi reaction, cyclohexanecarbox-amide, amide derivative

INTRODUCTION

Ugi reaction one of most important reactions in organic synthesis based on the four –chemical compound which is react together so this reaction [1,2] [multi component reaction, MCRs], the use of multi component reaction is expand in contemporary chemical biology and medicinal chemistry and developed to synthesized diverse type of drugs. This reaction very strong and include condensation of four compound (Amine, Aldehyde, Carboxylic acid, isocyanides) [3,4] at the end of MCRs we will collect substituted peptide as seen in **Figure 1**.

The [isocyanides] is unlike the other three compounds is commercially restricted so its formed by pulling out [H_2O] [7,8] using dehydrating agent of *Formamide* derived from Amine as seen in **Figure 2**.

The reaction depends on the nature of Carboxylic acid. For example, the Carboxylic acid formed (α-Amino acyl amide) this reaction become so wide and more interested by isolation of functionalize structure generating of isonitrile compound which used as intermediate to the schistosomiasis drug [5,6].

EXPERIMENTAL WORK

First-step we use three-necked, round-bottom flask [400 ml], side-neck equipped with pressure equalizing dropping funnel [50ml], and the middle neck equipped with thermometer.

Then added the mixture of [7.12 g, 45mmol]], [N-(phenethyl)formamide] and [15ml], [Et_3N] dissolved in [45ml], [DCM], the solution stirred slightly with string bar and cooled to [-10 °C] by using an ethanol ice bath.

Second-step adding drop- wise to the stirring [triphosgene], [5.39 g, 20mmol] in [DCM], [19ml] for 30 min by dropping funnel. The color of mixture become dark (red-brown) and continuing stirring at [-10 ^{0}C] for more 30 min after addition.

Third-step by using one necked-round bottom added the mixture [Creatinine] [5.2g 52mmol], with [Formaldehyde], [1.50g, 50mmol] dissolved in [50 ml Methanol]. Condensation for (16hrs) to (80 ^{0}C) in oil bath with continuous stirring [9,10].

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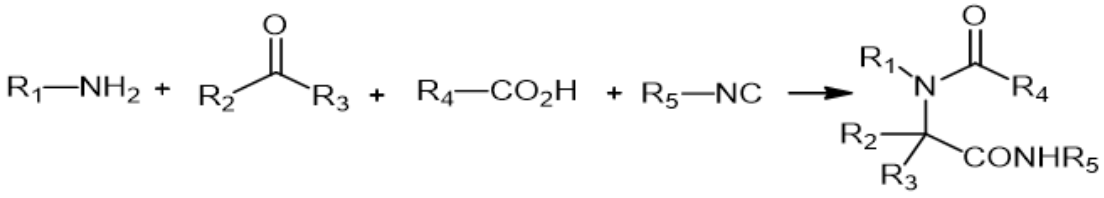


Figure 1. Reaction scheme of three-necked, round-bottom flask

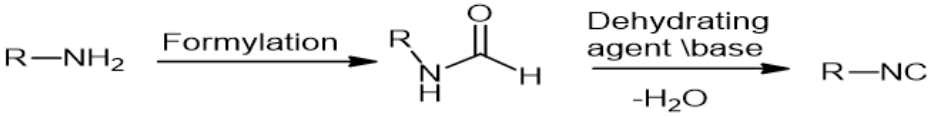


Figure 2. Reaction scheme of adding drop-wise to the stirring

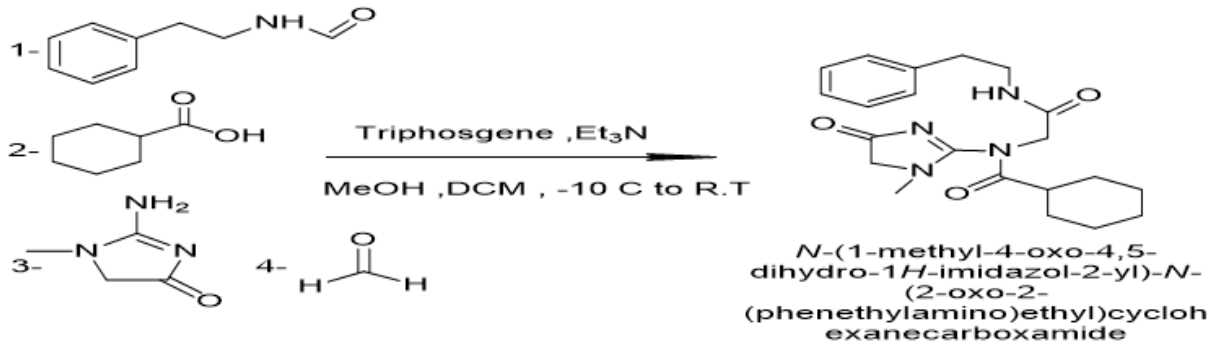


Figure 3. Reaction scheme of one necked-round bottom added the mixture

The result solution cooled of and added to it [Cyclohexane Carboxylic acid], (6.7g, 52mmol). The added the [MeOH], [50ml] for formation of [isocyanides] at [-10 ^{0}C] for 15 min. The heated up to the room temperature by continuous stirring [11].

Fourth-step after continues stirring at room temperature for (24 hrs) transferred the mixture to another one-necked-round-bottom (1000ml) after washing with (DCM) for rinse the flask. The solution concentrated by rotary evaporation [35 °C 7.1 mmHg] for removing the methanol [13].

After that transferred to (separation funnel) after dissolved in [DCM] then washed by water saturated with (sodium perchlorate) [2*20ml] then dried [sodium Sulfate Na_2SO_4] (10g) as drying agent then solvent removed under reduced pressure [14,15].

Collecting the result solution by [1000ml] round-bottom-flask and concentrated by rotary evaporation [35 ^{0}C 7.1 mmHg].

The final –step the crude product (red/brown) oil purified by silica gel chromatography by [Hexane and Ethyl estate as solvent.

Collected fractions concentrated by vacuum filtration for 6hrs (45°C 0.02 mm Hg) yield reddish brown solid crystals with purity [46%] as heterocyclic amid derivative seen **Figure 3** reaction equation.

RESULT AND DISCUSSION

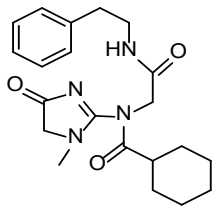
Reagent and solvents which used in this preparation are commercially supplied from (SigmaAldrich USA) and used without further purification. The reaction was monitored by [TLC EMD gel] visualized with iodine fume.

The final product was proofed by (infra-red) spectra [FT-IR SHIMADZU] the table below shows the FT-IR data (**Table 2**).

Table 1. Physical properties of formed compound

Chem. formula	m.p °C	Yield %	Time (hrs)	λ_{max}	Calculated% C H N O	Found % C H N O
$C_{21}H_{28}N_4O_3$	84.4-86.2C^0	46	24	450	65.60,7.34,14.52,12.48	66.02,7.15,13.98,12.50

Table 2. FT-IR data

Comp	ν (cm^{-1}) NHν	C=O ν Heterocyclic	C=Oν Free	C=Nν	Other
	3278	1694 -1690	1670- 1710	1631	2991-2944 CH Aliphatic 3100-3110 CH Aromatic

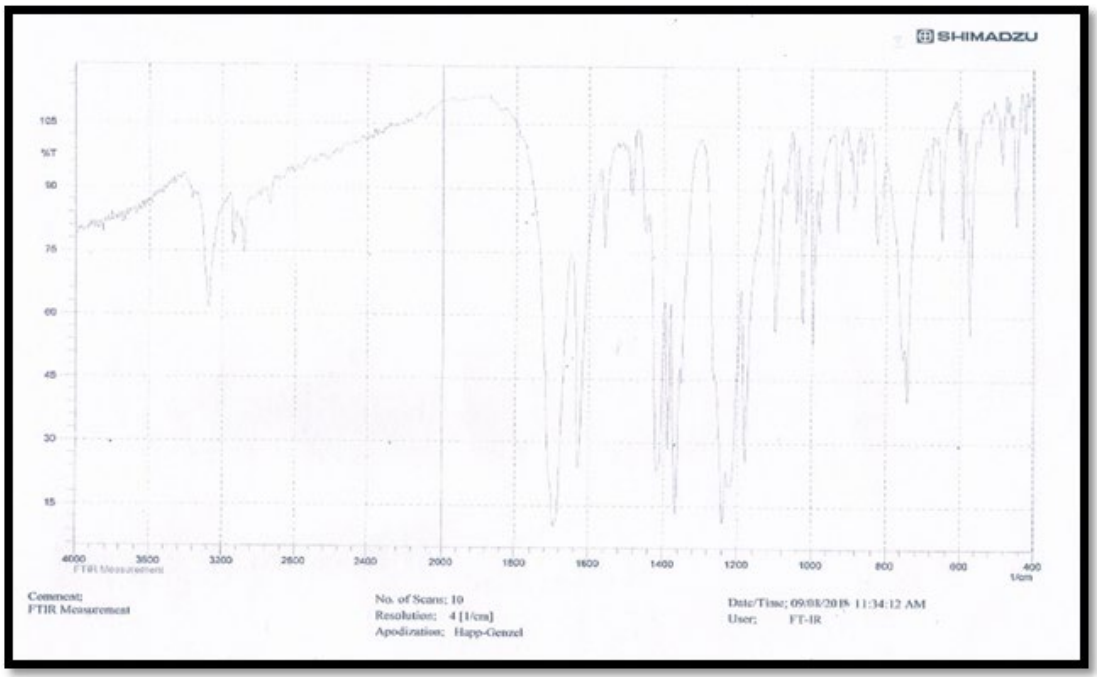
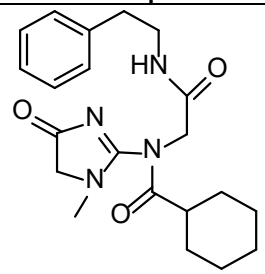


Figure 4. FT-IR spectra

Table 3. NMR data

Comp.	Solvent	(^{1}HNMR) Spectra (ppm)
	$CDCL_3$	,2.5,3.2(S,2H) 6.41,7.32(m,7H,Ar)δ 10.4(s,1H,NH)

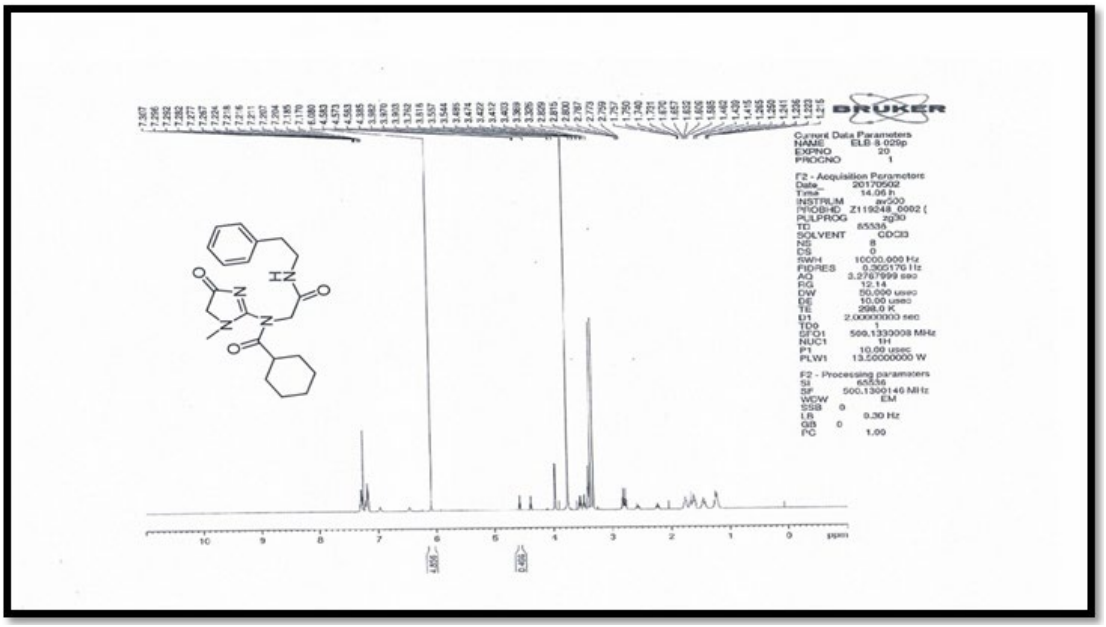


Figure 5. [1]HNMR SPECTRA

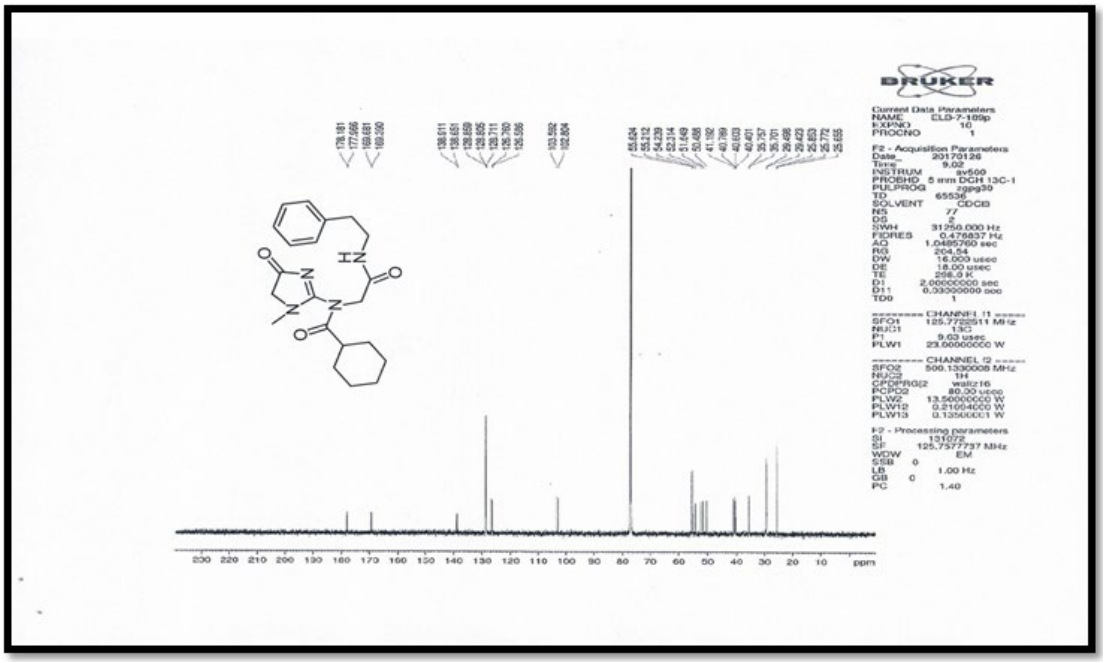


Figure 6. [13]CNMR SPECTRA

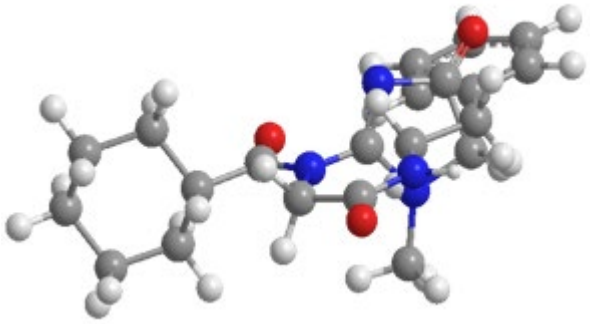


Figure 7. ORTEP diagram for compound

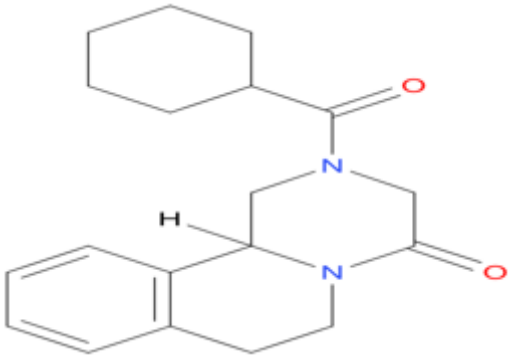


Figure 8. Praziquantel

Multi component reaction are very useful synthetic tools for combinatorial of (Ugi) four coupling reaction have great for accessing synthetic heterocyclic chemistry compound potential bioactive scaffolds building blocks for complex natural products and its analogues to test for their ability in treating various diseases such that (Praziquantel) was developed by [Bayer AG] medication used to treat a number of types of parasitic worm infections [12].

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