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SYNTHESIS AND EVALUATION OF TOLBUTAMIDE ASSISTED BY MICROWAVE OVEN

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ABSTRACT

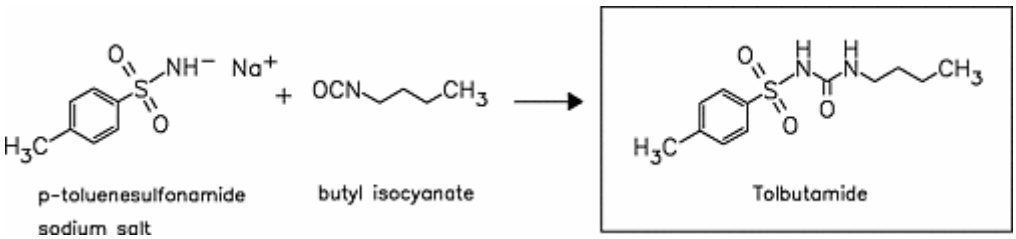
Microwave synthetic methods were devised for three lab reactions. The synthesis of tolbutamide. These reactions are all done in either general chemistry or organic chemistry. Under conventional heating methods, the tolbutamide synthesis requires heating at 55 °C for 30 minutes. The proposed microwave methods provide shorter reaction times (10 min. at 175 watts) while maintaining similar, if not better, yields. The tolbutamide synthesis was shortened to 7 minutes, and the Claisen condensation was shortened to 4.5 minutes. The microwave method produced 70.70% yield for tolbutamide, while conventional yield was 50.50%.

INTRODUCTION

Microwave chemistry allows such reactions to proceed at a fraction of the time, and boasts better yields. A microwave emits oscillating magnetic fields, causing polar molecules to rotate along with the magnetic field. This movement of molecules causes more interactions between molecules. Microwave reactions have been shown to be much faster, making these reactions useful. One such use is applying microwave chemistry in the undergraduate organic lab. Using a microwave in the organic chemistry lab can help students learn about optimization, while reducing wasted time in the lab. Students can run multiple reactions in the time it usually takes to run one reaction.[1] Most of the peptide synthesis is carried out on a solid phase and it has been observed that microwave irradiation enhances the deprotection, coupling, cyclization, condensation, isomerization, oxidation, reduction, cycloaddition, rearrangement, nucleophilic substitution and cleavage of chemical reactions. Based on the

highly efficient microwave heating technology, a series of potent and selective allosteric AKT kinase inhibitors were developed. Hese inhibitors were derived from a 2,3-diphenylquinoxaline. The present work introduces a detailed analysis of microwave assisted method of drug synthesis. also it will gives the difference between conventional and microwave heating method of drug synthesis.[2]

REACTION



$C_7H_9NO_2S$ (171.22gm/mol) C_5H_9NO (99.13gm/mol) $C_{12}H_{18}N_2O_3S$ (270.35gm/mol)

PRINCIPLE

Microwave assisted syntheses of Tolbutamide for the organic chemistry lab. In organic chemistry, many synthesis take hour under normal heating condition. Microwave chemistry allowed such reaction to proceed at a fraction of the time, and boast better yield. A microwave emits oscillating magnetic field, molecule cause more interaction between molecules. Microwave reactions have been shown to be much faster. Making thesereaction useful. One such use is applying microwave chemistry in the undergraduate organic lab. Using a microwave in the organic lab can help student learn about optimization. Tolbutamide is used together with diet and exercise to improve blood sugar control in adults with type 2 diabetes mellitus. Tolbutamide is not for treating type1 diabetes. Tolbutamide may also be used for purposes not listed in this medication guide.[3]

MATERIAL AND METHODS

SYNTHESIS OF TOLBUTAMIDE [CONVENTIONAL][4,5]

Procedure

1. About N-butyl Isocynate (1m mol /0.992gm) and triethylamine (1.2m mol/0.1214gm) in a round bottom flask containing 10ml of tetrahydrofuran, kept in an ice bath.

2. To the above mixture P-toluene sulfonamide (1m mol/0.171gm) was added drop wise at 0℃ .

3. After completing the addition the temperature was suddenly raised to 35-45℃ and stirred for 3-4 hrs.

4. Then the solution was filtered.

5. The product was separated and dried.

6. Then it was recrystallized by using Diethyl Ether.

Observation for N-butyl Isocynate

Weight of butter paper	0.25gm
Weight of butter paper +sample	1.25gm
Weight of butter paper (after transfer sample)	0.25gm
Weight of sample	1.00gm

Calculation

Theoretical yield

Molecular weight of P-Toluene Sulfonamide (reactant) $C_7H_9NO_2S$

12X7+1X9+7X1+14+16X2+32 =171

Molecular weight of Butyl-isocyanides (reactant) C_5H_9NO

12×5+1×9+14+16 = 99

Molecular weight of tolbutamide (product) $C_{12}H_{18}N_2O_3S$

$12 \times 12 + 1 \times 18 + 14 \times 2 + 16 \times 3 + 32$ =270

Theoreticlyield$= \frac{\text{molecular wt. of product}}{\text{molecular wt. of reactant}} \times \text{weight of sample}$

$= \frac{270}{270} \times 0.99 = 0.99g$

Theoretical yield = 0.99g Practical yield = 0.5g

Percentage(%)yield = $\frac{Practicalyield}{Theroticalyield} \times 100$

$= \frac{0.5}{0.99} \times 100 = 50.50\%$

Percentage (%) yield = 50.50%

SYNTHESIS OF TOLBUTAMIDE [MICROWAVE OVEN][6,7]

Procedure

1. About N-butyl Isocynate (1m mol/0.992gm) and triethylamine (1.2m mol/0.1214gm) in a round bottom flask containing 10ml of tetrahydrofuran, kept in an ice bath.

2. To the above mixture P-toluene sulfonamide (1m mol/0.171gm) was added drop wise at 0℃ .

3. After completing the addition the temperature was suddenly raised to 35-45℃ and stirred for 3-4 hrs.

4. Then the solution was filtered.

5. The product was separated and dried.

6. Then it was recrystallized by using Diethyl Ether.

OBSERVATION

Weight of butter paper	0.25
Weight of butter paper +sample	1.27
Weight of butter paper (after transfer sample)	0.26
Weight of sample	1.01

Calculation

Theoretical yield = $\frac{molecularwt.ofproduct}{molecularwt.ofreactant} \times weightofsample$

Theoretical yield = 0.99g

Practical yield = 0.7g

Percentage (%) yield = $\frac{Practicalyield}{Therotically ield} \times 100$

= $\frac{0.7}{0.99} \times 100$ =70.70%

Percentage (%) yield =70.70%

RESULTS

Evaluation of Tolbutamide [Conventional & Microwave]

Physicochemical characterization

S. N.	Parameters	Observation
1.	Color	White
2.	Odour	Odourless
3.	Appearance	Crystalline powder
4.	State	Solid

Flame test

Procedure: Place about 1g of the compound on the spatula. Heat it gently at first & finally to dull redness.

To observe-

A) Whether substance melts, explosive or flammable and the nature of flame.

B) Whether gases or vapors are evolved, and their odour.

C) Whether the residue fuses.

Positive –Tolbutamide is aromatic in nature.

Observation-The test is positive (blackish flame), Aromatic in nature.

Solubility

S.N.	Procedure	Observations
1.	Sample +Water	Insoluble
2.	Sample +Dimethyl carbonate, Ethanol, Choroform	Soluble

Melting point

Observation [Conventional]

S.N.	Burette reading		End point
	Initial	Final	
1.	122^0C	124^0C	124-126^0C
2.	126^0C	128.5^0C	

Observation [Microwave]

S.N.	Burette reading		End point
	Initial	Final	
1.	124^0C	126^0C	126-128^0C
2.	126^0C	128^0C	

Melting point of tolbutamide (conventional) -124^0C -126^0C

Melting point of tolbutamide (microwave) -126^0C -128^0C

pH determination

pH [Conventional] is 3.4 pH [microwave] is 3.2.

For Sulphated Ash

Weight of crucible	18.97g	Weight of crucible after ignition (A)	19.720g
Weight of crucible +sample	19.97g	Weight of crucible after ignition (B)	19.722g
Difference = B – A 19.722- 19.721= 0.001g =0 .1%			

Sulphated Ash Value [conventional & microwave] = 0.1%

For Loss on drying [microwave]

Weight of the weighing bottle	37.11g
Weight of the weighing bottle+ sample	38.11g
Actual weight of the sample	1.0g [W2]
Weight of the weighing bottle+ sample after drying	37.16g
Weight of the dry sample	0.95g [W1]
Loss of Drying = W2 – W1 = 1- 0.95 = 0.005	
Loss of Drying [%] = $0.005 \div 1 \times 100$ = 0.5%	

For Loss on drying [conventional]

Weight of the weighing bottle	35.1o g
Weight of the weighing bottle+ sample	36.10 g
Actual weight of the sample	1.0g [W2]
Weight of the weighing bottle+ sample after drying	35.19 g
Weight of the dry sample	0.91g [W1]
Loss of Drying = W2 – W1 = 1- 0.91 = 0.009	
Loss of Drying [%] = $0.009 \div 1 \times 100$ = 0.9%	

Limit test

S.N.	Limit Test	Observation	Inference
1.	Chloride Test	Opalescence produce is not more than std solution	Test is positive
2.	Sulphate Test	Opalescence produce is not more than std solution	Test is positive
3.	Arsenic Test	Any strain produce on mercuric chloride paper is not more intense than std solution	Test is positive
4.	Heavy metal Test	Color produced is not more than intense than std solution	Test is positive

Assay of Tolbutamide

Observation for assay: [conventional & microwave]

S.N.	Titration for	Burette reading		End point
		Initial	Final	
1.	Sample: 0.5g tolbutamide +40ml ethanol +add 20 ml water +titrate with 0.1M NaOH +Phenolphthalein indicator.	0.00ml	2.9ml(conventional) 3.6ml(microwave)	Color change from pink to orange
2.	Blank:-40ml ethanol + add 20 ml water + titrate with 0.1M NAOH +Phenolpthalein indicator	0.00ml	1.0ml(Conventional) 1.5ml (microwave)	Color change from pink to orange

Factor**:** Each ml of 0.1 N NaOH ≅0.02042g of $C_9H_8O_4$

Percentage purity(conventional) = 77.59% Percentage purity(microwave) = 85.76%

Standardization of 0.1 N NaOH

Normality of NaOH= 0.12 N

Charecterization: Element detection

Test	Observation	Inference
Test for Nitrogen	Blue color ppt.	Test is Positive
Test for Halogen	ppt not observed	Test is Negative
Test for Sulphur	Violet colored observed	Test is Positive

Rationale [Conventional & Microwave]

Particulars	Conventional	Microwave
Time	30-45 min	7- 10 min
% Yield	50.50%	70.70%
Eco friendly	No	Yes

RESULT AND DISCUSSION

Under the conventional condition, n-butyl iso-cynide and p-tolune sulphonamide are heated at 55 °C for 30 min. The chemical synthesis will be part of the effort for sustainable developement. Microwave assisted synthesis has revolutionized chemical synthesis. Small molecules can be built in fraction of the time required by conventional mathods. The basic mechanisms observed in microwave assisted synthesis are dipolar polarization and conduction. Microwave-assisted synthesis are provides clean synthesis with the advantages of enhanced reaction rates, higher yields, greater selectivity and economic for the synthesis of a large number of organic molecules, which have provided the momentum for many chemists to swish from conventional heating method to microwave assisted chemistry. Using conventional heating tolbutamide was isolated with a yield of 77.59.% while the shorter microwave method resulted in a comparable 85.76% yield.

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