International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

Comparative Analysis of ZnO Catalyzed Synthesis of β- Acetamido Ketones using Classical & Novel Approaches

Shahana Ehsan[*1], Tahira Saghir[2], Bushra Khan[3], Warda Tul Zahra[4]

[*]Department of Chemistry, Lahore College for Women University, Jail Road, Lahore, Pakistan
[2, 4]Central Lab., Lahore College for Women University, Jail road Lahore, Pakistan
[3]Head of Chemistry Dept., Lahore College for Women University, Jail road, Lahore, Pakistan

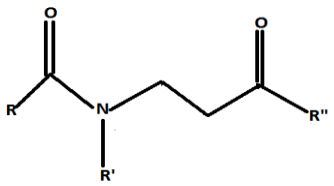
Abstract: ***β-acetamido ketones are included in the bioactive class of compounds which have immense versatility and importance in drug chemistry and also act as building blocks in various biological and pharmacological active compounds. This study will report the simple, rapid and efficient one-pot four component synthesis of β –acetamido ketones using benzaldehyde derivatives, acetophenone derivatives, acetyl chloride and acetonitrile as reactive species while ZnO as catalyst. Therapeutic rationale has stimulated the efforts to bring out the methods which consume less time and produce high yield. Various physical properties were studied such as color, appearance and melting point. The remarkable advantages offered by this method are mild reaction conditions, simple procedure, short reaction times and good yield.***

Keywords: β-acetamido ketones, ZnO, multicomponent reactions, microwave, benzaldehyde

1. Introduction

In recent years microwave assisted synthesis has emerged a new tool in organic synthesis. This methodology also considered as important technique in green chemistry too because of it is more environment friendly. The use of microwave irradiations also remove the problems of decomposition of substrate or products during the reaction due to the prolong heating. While using conventional technique of organic synthesis usually require more thermal treatment, deadly apparatus setup, which result in high cost process and excessive use of the solvent that leads to environmental pollution.[1]

β- acetamido ketones class comprises ketones with β-position and to these position, acetamide functional groups are attached.



β- acetamido ketone

β-acetamido ketone is the leading class among the list of the novel hetero compound, that have the center of interest of the researchers. Their biological and pharmaceutical properties reflect their novelty. [2]

β-acetamido carbonyl compounds are valuable building blocks for many biological and pharmaceutically important compounds, for example for the preparation of 1, 3-amino alcohols, neopolyoxines and antibiotic nikkomycins. The structural units common in natural nucleoside antibiotics are the molecules, for which the beta acetamidoketoester act as substantial starting materials. So, synthesis of β-acetamido ketones has attracted much consideration in organic synthesis. [2]

Multicomponent reactions (MCRs) offer substantial advantages over conventional linear type synthesis and are preferred over other reactions, as they provide useful products in a single step by the creation of several new bonds without separation of any intermediate thus reduce the time and save both energy and the raw material a large number of organic molecules. [3]

The present research work was established to fabricate β-acetamido ketones by opting classical method reported in literature along with microwave technique, a novel approach, in order to bring out the better method from the comparison of both approaches. Here in the method, ZnO(an inorganic white powdered compound which is insoluble in water) is used as a catalyst for the reaction. The reported process is advantageous over known methods in terms of short reaction time, ease of reaction protocol and work up.

2. Literature Survey

A variety of β-acetamido ketones and keto esters has been prepared via a three component coupling of aromatic aldehydes, enolizable ketones or ketoesters and nitriles by using $ZnSO_4$and acetyl chloride for catalytic purpose [4] and another varietyof β-acetamido ketones has been synthesized by employing BF_3/Et_2O catalytic process under microwave irradiation [5]. Similarly, fabrication of this important reactive intermediate is also reported in literature by using different catalysts like: heteropolyacid [6], potassium dodecatungstocobaltatetrihydrate ($K_5CoW_{12}O_{40}.3H_2O$) [7], $FeCl_3.6H_2O$ [8], sulfamic acid [9], AgOTf [10], $Zr(HSO4)_4$& $Mg(HSO4)_4$ [11], boric acid[12], $CeCl_3.7H_2O$ [13], $FePO_4$ [14] and many others.

3. Materials and Methods

All chemicals used in the synthesis were of analytical grade from Merck and Fluka. Microwave oven DW-180, 2450 MHz, 950 W was used for synthetic purpose.

β-acetamido ketones were synthesized by both reported conventional methods as well as using novel approach i.e.: microwave technology. The results obtained by both strategies were compared for the evaluation of advantages claimed by microwave assisted synthesis.

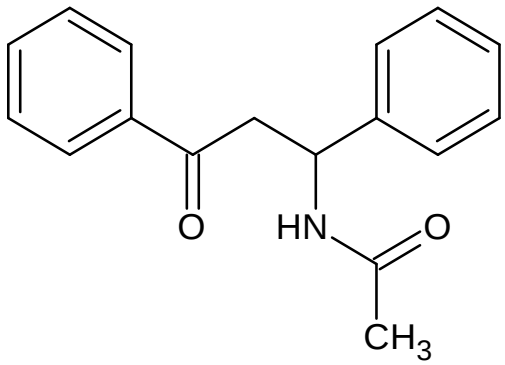
The synthesis of compounds was established in single step i.e.: condensation of aromatic aldehyde derivatives and ketone derivatives by employing ZnO as a catalyst.

3.1. Conventional Synthesis

3.1.1. General procedure for conventional synthesis of derivatives of β-acetamidoketones

A mixture of the aryl aldehyde (1 mmol), aryl ketone (1 mmol), acetyl chloride (2 mL) and acetonitrile (2 mL) in the presence of ZnO (0.5 g) was heated at 80°C with stirring for 5-7 h.The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was poured into ice cold water (50mL).After dissolving precipitate in dichloromethane, ZnO was separated by filtration. Organic layer was engaged on silica gel. Purification done by column chromatography using ethyl acetate and ether 9:1.

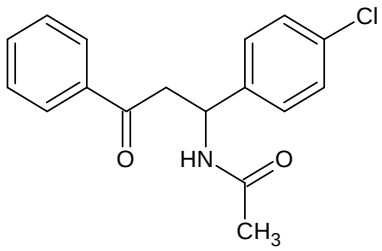
3.1.2. Conventional synthesis of N-(1, 3-diphenyl-3-oxopropyl) acetamide (P1)



N-(3-oxo-1,3-diphenylpropyl)acetamide

Solution of benzaldehyde (1.063mL), acetophenon (1.063mL), acetyl chloride (2mL) and zinc oxide (0.5 g) poured in acetonitrile (2mL)and kept for stirring at 80°C for 7 h. At the completion of reaction that checked by TLC, reaction mixture poured into ice cold water (50mL).After dissolving precipitate in dichloromethane, ZnO was separated by filtration. Organic layer was engaged on silica gel. This material purified by column chromatography using ethyl acetate and ether 9:1.

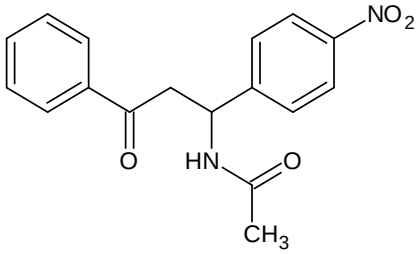
3.1.3. Conventional synthesis of N-[1-(4-chlorophenyl)-3-phenyl-oxopropyl] acetamide (P2)



N-[1-(4-chlorophenyl)-3-oxo-3-phenylpropyl]acetamide

To a stirred suspension containing 4-cholorobenzaldehyde (1.073mL), acetophenon (1.074mL), acetonitrile (2.021mL), zinc oxide (0.5g) and acetyl chloride (2.026mL)collected and stirred at 80°Cfor 5.5 hrs. TLC was done to check accomplishment of reaction. Mixture transferred into a beaker containing ice cold water (50mL). Precipitate dissolved in dichloromethane (DCM) and zinc oxide was isolated by filtration. The organic layer immersed on silica gel. Purification done with the help of Column chromatography.

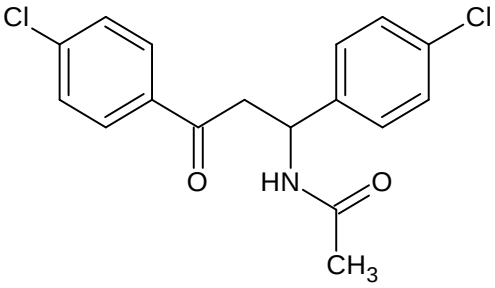
3.1.4. Conventional synthesis of N-[1-(4-nitrophenyl)-3-oxo-3-propyl]acetamide(P3)



N-[1-(4-nitrophenyl)-3-oxo-3-phenylpropyl]acetamide

Acetonitrile (1.964mL), acetophenone (0.878mL), 4-nitrobenzaldehyde (0.912mL), acetyl chloride (1.893mL) and zinc oxide (0.0391g) was mixed and stirred at 80°C for 6 hr. End of reaction examined with TLC. After this mixture was transferred in cold water (50mL). The solid dissolved in the dichloromethane. Then filtration was carried out, the organic layer kept on silica gel. The purification process carried out with column chromatography.

3.1.5. Conventional synthesis of N-[1, 3(4-chlorophenyl)-3-oxopropyl]acetamide (P4)



N-[1,3-bis(4-chlorophenyl)-3-oxopropyl]acetamide

4-chloroacetophenon (1.213mL), acetonitrile (2.016ml), zinc oxide (0.0423g), 2-chlorobenzaldehyde (1.039ml) and

acetyl chloride (1.970ml) mixed and stirred for 5h at 80°C.At the end of reaction that tested by TLC. Reaction material transferred in cold water. Precipitate dissolved in dichloromethane and filtration was performed. Oily layer immersed on the silica gel. Further product purified through column.

3.2. Microwave Assisted Synthesis

3.2.1. General procedure for synthesis of derivatives of β-acetamidoketones under microwave irradiation

Aryl aldehyde (1 mmol), aryl ketone (1mmol), acetonitrile (4mL), acetyl chloride (2mL) and zinc oxide (0.5g) were mixed and subjected to microwave radiation for 2min. Then mixture was dispensed into ice cold water (50mL). Precipitate extracted with dichloromethane. Filtration was done, organic layer dried on silica gel. Pure product obtained through column chromatography using two solvents ether and ethyl acetate.

3.2.2. Synthesis of N-(1, 3-diphenyl-3-oxopropyl) acetamide under microwave irradiation (P1)

Benzaldehyde (1.063mL), acetophenon (1.063mL), acetonitrile (4mL), acetyl chloride (2mL) and zinc oxide (0.5g) were mixed and subjected to microwave radiation for 2min. Then mixture was dispensed into ice cold water (50mL). Precipitate extracted with dichloromethane. Filtration was done, organic layer dried on silica gel. Pure product obtained through column chromatography using two solvents ether and ethyl acetate.

3.2.3. Synthesis of N-[1-(4-chlorophenyl)-3-phenyl-oxopropyl] acetamide under microwave irradiation (P2)

4-chlorobenzaldehyde (1.067Ml), acetonitrile (2.102mL), acetophenon (1.102mL), zinc oxide (0.5g) and acetyl chloride (2.178mL) mixed and subjected to the microwave radiations for 1.5min. Reaction mixture transferred into ice water (50mL). Precipitate dissolved into dichloromethane. Filtration carried out, organic layer dried on silica gel and product purified through column chromatography. Solvents of column chromatography were ether and ethyl acetate (9:1).

3.2.4. Synthesis of N-[1-(4-nitrophenyl)-3-oxo-3-propyl] acetamide under microwave irradiation (P3)

Reactants acetophenon (0.834mL), acetonitrile (1.673mL), 4-nitrobenzaldehyde (0.867mL), acetyl chloride (1.736mL) and zinc oxide (0.0435g) were mixed and exposed to the microwave radiations for1.5min. The mixture shifted into 50ml cold ice water. Precipitate extracted in dichloromethane. Solution was filtered, the organic layer captivated on silica gel. Column chromatography was done for purification.

3.2.5. Synthesis of N-[1, 3(4-chlorophenyl)-3-oxopropyl]acetamide under microwave irradiation (P4)

4-chloroacetophenon (1.511ml), acetonitrile (1.916ml), zinc oxide (0.0497g), 2-chlorobenzaldehyde (1.371ml) and acetyl chloride (2.270ml) were mixed and exposed to microwave radiations for 1min. After completion, material poured into ice cold water(50mL). Precipitate dissolved into dichloromethane. The solutions undergo the filtration technique to collect the zinc oxide. Organic material enthralled at silica gel. Separating technique, column chromatography, performed to collect the pure product.

4. Results & Discussion

The percentage yields of synthesized compounds by both conventional method as well as microwave approach and time taken by the reactions as well as melting points of the fabricated compounds was recorded (Table 1, Table 2 and Table 3 respectively).

Table 1: Percentage yield of fabricated compounds

Compound	Percentage yield (%)	
	Conventional	Microwave
P1	76	83
P2	78	83.9
P3	81.56	88
P4	89	92

Table 2: Reaction time of compounds

Compound	Time (s)	
	Conventional	Microwave
P1	25, 200	110
P2	21, 000	80
P3	21, 600	90
P4	18, 000	70

Table 3: Melting points of Compounds

Compound	Melting points(°C)	
	Conventional	Microwave
P1	102	104
P2	148	147
P3	151	153
P4	161	159

UV spectra were recorded within the range of 200-600 nm on Hitachi U-2800 spectrophotometer.

Table 4: UV/Vis data of synthesized compounds

Compound	Conventional λ_{max}(nm)	Microwave λ_{max}(nm)
P1	228, 268	224, 266
P2	218, 278	218, 281
P3	214, 288	216, 282
P4	216, 267	211, 246

UV-Vis data for derivatives of β-acetamido ketones synthesized by both conventional and microwave irradiation is in close approximation with each other. The peaks at lower values are result of the attachment of amino group to the carbonyl that shifted the absorption due to the n-π* transition to a shorter wavelength while the other

peaks at higher values are consequence of π-π* transition occurring due to the presence of aromatic ring.

FTIR spectra of all fabricated compounds were recorded on Midac USA M-2000 FTIR spectrophotometer. (Table 5a, 5b). FTIR spectra for all synthesized compounds showed approximately similar values for conventional and microwave-assisted method. The FTIR spectra showed significant bands in finger print region; the peaks at region of 1250-1280 cm^{-1} showed the C==O stretch for amides. Then the next IR bands in the region of 3000-325ocm^{-1} confirmed the amide functional group in the products. Aromatic ring presence was indicated by the peaks in 1600-1400cm^{-1}region. The carbonyl group existence was cleared with the peaks at region of 1650-1750 cm^{-1}. A very strong peak at region of 700-780 $cm^{-1}$was observed due to C-Cl stretch in the spectrum of **P2**. In **P3** spectrum, nitro group presence was showed by the peaks in the region of 1500-1580 $cm^{-1}$and in **P4** spectrum, the stretch due to Cl was appeared at peak 780-784 cm^{-1}.

Table 5 (a): FTIR data of compounds synthesized by conventional method

Compound	Conventional Wave number (cm^{-1}) Absorption intensity
P1	1260.17, 3251.34, 1600-1400, 1720.56, 1260.17, 3108.57, 1593.79, 744.67
P2	1260.17, 3251.34, 1600-1400, 1720.56, 1260.17, 3108.57, 1593.79, 744.67
P3	1256.67, 3014.34, 1600-1400, 1730.56, 1260.17, 3148.57, 1576.23, 699.24
P4	1260.67, 3251.34, 1600-1400, 1630.56, 1496.10, 3178.34, 1687.63, 784.67

Table 5 (b): FTIR data of compounds synthesized by microwave-assisted method

Compound	Microwave Wave number (cm^{-1}) Absorption intensity
P1	1256.22, 3191.34, 1600-1400, 1700.56, 1278.17, 3108.57, 1613.79, 742.67
P2	1280.17, 3051.34, 1600-1400, 1700, 1247.17, 3258.57, 1253.79, 738.67
P3	1275.31, 3141.67, 1600-1400, 1730.56, 1260.17, 3128.07, 1511.79, 714.67
P4	1260.17, 3251.34, 1600-1400, 1700.56, 1380.37, 3038.57, 1623.22, 780.11

Mass spectra of all compounds synthesized by conventional as well as microwave irradiation method were taken by **GCMSSchimadzo QP-2010 Spectrometer** (Table 6).

Table 6: Mass spectral data of synthesized compounds

Compound	Formula		
		Conventional	Microwave
P1	$C_{17}H_{17}NO_2$	268 (M+H)	268 (M+H)
P2	$C_{17}H_{16}ClNO_2$	303 (M+H)	303 (M+H)
P3	$C_{17}H_{15}N_2O_4$	313(M+H)	313(M+H)
P4	$C_{17}H_{14}C_{l2}NO_2$	320 (M+H)	320 (M+H)

5. List of Abbreviations

Sr. No.	Compound Name	Abbreviation
1	N-(1, 3-diphenyl-3-oxopropyl) acetamide	P1
2	N-[1-(4-chlorophenyl)-3-phenyl-oxopropyl] acetamide	P2
3	N-[1-(4-nitrophenyl)-3-oxo-3-propyl]acetamide	P3
4	N-[1, 3(4-chlorophenyl)-3-oxopropyl]acetamide	P4

6. Conclusion

This reported work was designed to synthesize important reactive intermediate i.e.; β- acetamido ketones using simple and easily available catalyst (ZnO) under microwave irradiation. Furthermore, a comparison was established between a conventional and a novel (microwave) approach in order to signify the importance of microwave method. Reduced reaction time and improved yield with high purity under microwave technique are the advantageous points over conventional method depicting that former technique can be a first choice of synthetic chemists.

The structure elucidations of fabricated compounds were carried out via FTIR, UV/Vis & GC-MS.

7. Future Scope

Microwave-assisted synthesis has taken its distinct position in Organic Chemistry to synthesize a large number of organic compounds because of its enormous advantages. Use of this green approach gives better results in reduced time and cost. It will become a key source to synthesize a large number of compounds on industrial scale.

References

[1] Meketa, A.S.; Samita, J.; Desai, K.R., Scholars Research Library, 4 (1), 645-661, 2012
[2] Sunil, N.D.; Nagnnath, D. K.; Jaiprakash, N. S., Green Chemistry, 5, 643-648, 2012.
[3] Rafiee, E.; Paknezhad, F.; Shahebrahimi, S.; Eavani, S.; Rashidzadeh, S., Journal Of Molecular Catalysis, 282, 92-98, 2008.
[4] Dinanath, D. P.; Dnyandeo, K. M.; Gurumeet, C. W., International Journal of Institute Pharmacy and Life Science, 1, 212-213, 2011.
[5] Sunil, N.D.; Nagnnath, D. K.; Jaiprakash, N. S., Green Chemistry, 5, 643-648, 2012.
[6] Ali, J.; Majid, H. H.; Fatemeh, F.B., Springer-verlag, 143, 831-834, 2011
[7] Lingaiah, N.; Rajashaker, B. and Rakesh, P., Applied Catalysis, 332, 304-309, 2007.
[8] Abu, T. K; Lokman, H. C.; Tasneem, P. and Asif, A.,, Tetrahedron letters, 47, 8137-8141, 2006.
[9] Majid, M.H.; Leila, R.; Fatemeh, D. and Fatemeh, F. B., Catalysis Communications, 8, 289-291, 2007.

[10] Rameshwar, P. P. and Yong, R. L., Bull. Korean Chem. Soc., 11, 3559-3563, 2012.
[11] Ahmad, R.; Maryam, S.; Motahareh, H., Turk J. Chem., 33, 751-758, 2009.
[12] Zahed, K. and Korosh, M., The Scientific World Journal, 47, 268-270, 2012.
[13] Lokman, H. C.; Abu, T.K.; Tasneem, P.; Mohammad, A.A., Tetrahedron Letters, 47, 8137-8141, 2006.
[14] Farahnaz, K. B.; Sara, S., Eur. Chem. Bull., 2, 832-835, 2013

Authors Profiles

Dr. Bushra Khan received the MSc and PhD degree in analytical chemistry from Punjab University Lahore Pakistan. Now she is a Professor of Meritorious, Dean of natural sciences and Head of chemistry department of Lahore College for women University Lahore. She is teaching and conducting research of graduate and postgraduate students. Her research papers have been published in various journals.

Dr. Shahana Ehsan received MSc and PhD degree from Punjab University and Lahore College for women University Pakistan respectively. Now she is assistant professor and her field of research is organic chemistry especially synthetic Chemistry.

Mrs. Tahira Saghir did her MS in organic chemistry from Lahore College for Women University, Lahore, Pakistan. She is a PhD scholar of Lahore College

Ms. Warda Tul Zahra did her BS in organic chemistry with distinction, now she is student of MS