International Journal of Drug Delivery 6 (2014) 326-328
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

# One-Pot Multicomponent Synthesis of β-Acetamido Ketones Using $BF_3$-$Et_2O$ as Catalyst

Preeti Rawat[1], Pinki Rawat[1], Piyush Kumar[2]

*Corresponding author:

Preeti Rawat

[1] Department of Pharmaceutical Sciences, Singhania University, Jhujhunu-333515, Rajasthan, India.
[2] National Institute of Pharmaceutical Education & Research, Raebareli-229010, Uttar Pradesh, India.

## Abstract

Starting from different ketones 1a-1f, aldehyde 2a-2g, and acetonitriles 3a-3d we synthesize some bioactive β- Acetamido carbonyl compounds 4a-4h. We also attempted to synthesize these compounds by using phenylacetone and deoxybenzoins in place of ketones to afford the products 4i-4j. $^1$H-NMR spectra are presented. On the basis of QSAR studies, some compounds were tested for their anti-thrombotic activity in mice. Compound 4f, 4h and 4j were found to exhibit less percentage protection.

**Keywords:** Antithrombotic activity, β-Acetamido Ketone, Multicomponent reaction

## Introduction

During the past few years, multicomponent reactions (MCRs) have proved to be remarkably successful in generating molecular complexity in a single synthetic-step operation [1-4]. These processes consist of two or more synthetic steps, which are performed without isolation of any intermediates, thus reducing time and saving both energy and raw materials. MCRs are powerful tools in modern drug-discovery processes and allow fast, automated, and high-throughput generation of organic compounds [5].

Multicomponent reactions (MCRs) are important for the achievement of high levels of diversity, as they allow more than two building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle [6]. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. Researchers have transformed this powerful technology into one of the most efficient and economic tools for combinatorial and parallel synthesis [7]. Due to their inherent simple experimental procedures and their one pot character, they are perfectly suited for automated synthesis. Multi-component, one-pot syntheses are also highly important because of their wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for preparation of drug-like molecules with several levels of structural diversity [8,9].

β- Acetamido ketones and esters are valuable building blocks for a number of biologically and pharmaceutically bioactive important compounds [10,11]. They could easily be converted to 1, 3-amino alcohols, which are precursors for the synthesis of several antibiotics such as nikkomycins or neopolyoxins [12]. Furthermore, a field of increasing interest is the synthesis of useful synthetic building blocks via MCR chemistry. For this reason, the discovery of novel MCRs is of interest [13-15].

Devising reactions that achieve multi-bond formation in one step operation is becoming one of the major challenges in stepeconomic synthesis. As an enabling technology, multicomponent reactions (MCRs) make it possible to access target molecules with greater efficiency and atom economy [16].

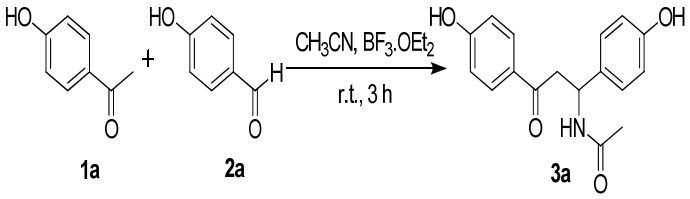
## Materials and Methods

All chemicals used in this research were purchased from sigma aldrich. The melting points of the synthesized compounds were measured with melting point analyzer Mel-Tem II. $^1$H NMR and $^{13}$C NMR spectra were run on Bruker Advance DPX 200/300 MHz spectrometer in $CDCl_3$ unless stated otherwise and TMS was used as internal standard. Silica gel 60–120 mesh was used as stationary phase to isolate the compounds.

### Experimental Procedure

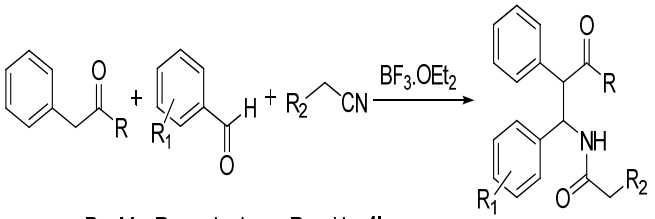
We developed a new synthetic methodology for the synthesis of β-acetamido carbonyl compounds using $BF_3.OEt_2$ as a reagent. Initially, we attempted the reaction between p-hydroxy acetophenone, p-hydroxy benzaldehyde and acetonitrile using $BF_3.OEt_2$ and successfully synthesized our desired compound (Scheme 1).

**Scheme 1**




Encouraged by the results, we used different ketones 1a-1f, aldehyde 2a-2g, and acetonitriles 3a-3d to synthesize more analogues and were succeeded to afford our desired products 4a-4h. We also attempted to synthesize these compounds by using phenylacetone and deoxybenzoins in place of ketones to afford the products 4i-4j (Scheme 2).

**Scheme 2**




R = Me, $R_1$ = *p*-hydroxy, $R_2$ = H, **4i**

R = *p*-methoxyphenyl, $R_1$= 3,4-dichloro, $R_2$ = 1-naphthyl, **4j**

All synthesized compounds were characterized by $^1$H and $^{13}$C-NMR and Mass spectroscopy. All the results are summarized in the Table 1.

## General procedure for the synthesis of β- Acetamido ketones (4a-4j)

Ketone and aldehyde (1:1 equivalent) are dissolved in acetonitrile. $BF_3.OEt_2$ was added to the reaction mixture. The reaction was refluxed for 3-6 hrs at 70-80˚C depending upon the reactants. The reaction was monitored by TLC. Acetonitrile was evaporated in the rotary evaporator. Ethyl acetate was added to this crude mixture and washed it with water for 2-3 times. The organic layer was dried over sodium sulphate and evaporates it under the reduced pressure. Purification of the compounds was carried out with silica gel column chromatography.

### N-[1,3-bis(4-hydroxyphenyl)-3-oxopropyl]acetamide (4a)

Yield: 96%; m.p. 102˚C; $^1$HNMR (400 MHz, $CDCl_3$): 5.45(s,1H), 6.74-6.77(d,2H), 6.85-6.88(d,2H), 7.19-7.22(d,2H), 7.80-7.92(m,5H)

### N-[1,3-bis(4-hydroxyphenyl)-3-oxopropyl]-2-(naphthalen-1-yl)acetamide (4b)

Yield: 94%; m.p. 145˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 3.3-3.5(m,2H), 4.00(s,2H), 5.50(s, 1H), 6.71-6.87(m,4H), 7.12-7.16(d,2H), 7.40-7.50(m,4H), 7.80-7.92(s,5H)

### N-[1,3-bis(4-hydroxyphenyl)-3-oxopropyl]prop-2-enamide (4c)

Yield: 92%; m.p. 137˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 3.33-3.58(m,2H), 5.51-5.55(t,1H), 5.61-5.65(m,1H), 6.21-6.26(t,2H), 6.74-6.76(d,2H), 6.83-6.86(d,2H), 7.19-7.22(d,2H), 7.86-7.89(d,2H)

### N-[(1E)-5-(4-hydroxyphenyl)-5-oxo-1-phenylpent-1-en-3-yl]acetamide (4d)

Yield: 93%; m.p. 150˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 1.95(s,3H), 3.23-3.41(m,3H), 4.89-5.09(t,1H), 6.21-6.32(m,1H), 6.49-6.57(d,1H), 6.83-6.89(m,2H), 7.18-7.37(m,5H), 7.89-7.90(d,2H)

### N-[(4E)-1-(4-hydroxyphenyl)-4-methyl-1-oxohept-4-en-3-yl]acetamide (4e)

Yield: 90%; m.p. 140˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 1.25(s,5H), 1.63(s,4H), 2.00(s,5H), 3.04-3.26(m,2H), 4.80(s,1H), 5.32(s,1H), 6.52(s,1H), 6.84-6.87(d,2H), 7.81-7.85(d,2H)

### N-[1-(5-bromo-2-methoxyphenyl)-3-(3,4-dichlorophenyl)-3-oxopropyl]-2-cyanoacetamide (4f)

Yield: 89%; m.p. 180˚C; $^1$H NMR (400 MHz, $CDCl_3$): 3.12-3.16(d,2H), 3.68(s,2H), 3.79-3.81(d,3H), 5.73(s,1H), 6.99-7.46(m,6H), 8.15(s,1H)

### N-[(5-chloro-2-nitrophenyl)(2,6-dioxocyclohexyl)methyl]acetamide (4g)

Yield: 85%; m.p. 145˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 1.78-1.82(t,2H), 1.9(s,3H), 2.31(s,3H), 2.49-2.50(m,4H), 5.27(s,1H), 6.35-6.37(d,1H), 7.32-7.35(d,1H), 7.75-7.78(d,1H), 7.85-7.89(m,1H), 8.42-8.43(d,1H)

### N-[(4-cyanophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)methyl]acetamide (4h)

Yield: 92%; m.p. 105˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 0.99(s,6H), 2.09(s,3H), 2.25(s,4H), 6.37-6.41(d,1H), 7.40-7.43(d,2H), 7.49-7.52(d,2H), 8.25-8.28(d,1H)

### N-[1-(4-hydroxyphenyl)-3-oxo-2-phenylbutyl]acetamide (4i)

Yield: 86%; m.p. 112˚C; $^1$H NMR (400 MHz, $CDCl_3$):: 1.63(s,2H), 1.93(s,4H), 2.15(s,3H), 3.34-3.38(m,1H), 4.25-4.30(d,1H), 4.37-4.43(d,1H), 4.67(s,1H), 5.46-5.51(d,1H), 5.63-5.69(d,1H), 6.54-6.58(d,2H), 6.76-6.80(d,2H), 6.94-6.98(d,2H), 7.12-7.44(m,9H)

### N-[1-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxo-2-phenylbutan-2-yl]-2-(naphthalen-1-yl)acetamide (4j)

Yield: 90%; m.p. 107˚C; $^{13}$C NMR (400 MHz, $CDCl_3$): 30.3, 42.3, 56.0, 56.8, 164.4, 171.4, 124.5, 127.5, 129.4, 131.6, 136.2, 141.8

## Results and Discussion

Conventional methods were used to carry out all the reaction steps. BF3/Et2O was used as catalyst to synthesize various β-Acetamido ketones derivatives (4a-4j). The desired compounds were prepared using ketone (1 equi.) and aldehyde (1 equi.), $BF_3.OEt_2$ in acetonitrile solvent under reflux at 70-80˚C for 3-6 hrs. Various β-acetamido ketones derivatives were synthesized using different substituted aldehydes (1a-1f), ketones (2a-2g) and acetonitrile (3a-3b) using optimized reaction conditions. The results are summarized in Table 1. The yields obtained were ranging from 85% to 96%.

Few compounds were tested for their antithrombotic activity in mice. Clopidogrel was taken as a standard oral anti-platelet drug which shows 60% inhibition in mice. Compound 4f, 4h and 4j were tested and found exhibiting less % protection which is 20, 22 and 10% respectively. Results are summarized in Table 2.

**Table 2: Antithrombotic activity results in mice**

| S. No. | Compounds | % Protection |
|---|---|---|
| 1 | **4f** | 20 |
| 2 | **4h** | 22 |
| 3 | **4j** | 10 |
| 4 | Clopidogrel | 60 |

## Conclusion

We have developed an efficient and improved three-component coupling reaction for the synthesis of β- Acetamido carbonyl compounds. The method offers several advantages such as short reaction times, simple reaction conditions and tolerance to a wide variety of reactants.

## References


[1]. Eibracht P, Schimdt J. Tandem Reaction Sequences under Hydroformylation Conditions: New Synthetic Applications of Transition Metal Catalysis. Chem Rev 1999; 99: 3329-66.

[2]. Ugi I. Recent progress in the chemistry of multicomponent reactions. Pure Appl Chem 2001; 73: 187-91.

[3]. Bagley MC, Cale JW, Bower. A new one-pot three-component condensation reaction for the synthesis of 2,3,4,6-tetrasubstituted pyridines. Chem Commun 2002; 1682-83.

[4]. Bora U, Saikia A, Boruah RC. A Novel Microwave-Mediated One-Pot Synthesis of Indolizines via a Three-Component Reaction. Org Lett 2003; 5: 435-38.

[5]. Weber L, The application of multicomponent reactions in drug discovery. Curr Med Chem 2002; 9: 1241-44.

[6]. Zhu J, Bienayme H. Multicomponent Reactions. Wiley: Weinheim 2005.

[7]. Beck B, Hess S, Domling A. One-pot Synthesis and Biological Evaluation of Aspergillamides and Analogues. Bioorg Med Chem Lett 2000; 10 (15): 1701-5.

[8]. Armstrong RW, Combs AP, Tempest PA, Brown SD, Keating TA. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. Acc Chem Res 1996; 29 (3): 123–131.

[9]. Terret NK, Gardner M, Gordon DW, Kobylecki RJ, Steel J. Combinatorial synthesis- the design of compound libraries and their application to drug discovery. Tetrahedron 1995; 51: 8135–8173.

[10]. Casimir JR, Turetta C, Ettouati L, Paris J. First application of the Dakin-West reaction to fmoc chemistry: Synthesis of the ketomethylene tripeptide fmoc-N -Asp(tBu)-(R,S Tyr(tBu)Ψ(CO-$CH_2$)Gly-OH. Tetrahedron Lett 1995; 36: 4797-4800.

[11]. Godfrey AG, Brooks DA, Hay LA, Peters M, McCarthy JR, Mitchell D. Application of the Dakin West Reaction for the Synthesis of Oxazole-Containing Dual PPAR /γ Agonists. J Org Chem 2003; 68: 2623–2632.

[12]. Dahn U, Hagenmaier H, Hohne H, Konig W.A, Wolf G, Zahner H. Metabolic Products of Microorganisms. Arch Microbiol 1976; 107: 143–160.

[13]. Ugi I, Werner B, Domling A. The Chemistry of Isocyanides, their Multicomponent Reactions and their Libraries. Molecules 2003; 8: 53-66.

[14]. Domling A. The discovery of new Isocyanide-based Multi-component Reactions. Curr Opin Chem Biol 2000; 4 (3): 318-23.

[15]. Weber L. Multi-component Reactions and Evolutionary Chemistry. Drug Discovery Today 2002; 7 (2): 143-47.

[16]. Zhu J, Bienayme H. Multicomponent Reactions. Wiley-VCH: Weinheim, Germany 2005.