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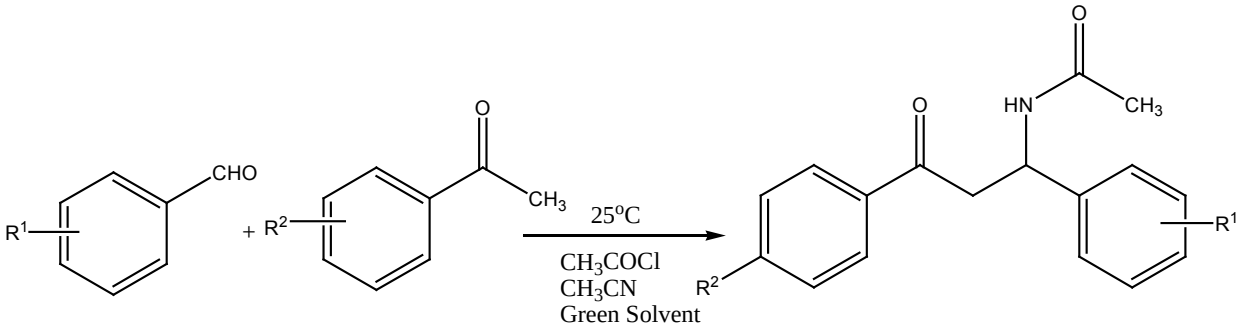

R^1=H,Cl,Me,OH,NO_2,OCH_3,$OCOCH_3$,
R^2=H,Me,Cl,4-NO_2,3-OMe,4-Cl,4-Br

I. Introduction

Multicomponent reactions (MCRs) provide useful products in a single step without isolation of any intermediates; they are preferred over the other reactions. The MCRs constitutes to single step procedures and non isolation of intermediate moiety which leads to the synthetic route representing saving of both energy and raw materials.[1] These reaction (MCRs) have emerged as one of the most useful tool for synthetic transformation in organic synthesis due to their wide application in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery. One of the important reason for up growing vitality of MCRs is their key role in organic chemistry in generation of high complex structure by simple one pot process.[2] MCRs owed to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production. The transformation of this useful technology into a most efficient and economic tools for combinatorial and parallel synthesis is done by many researchers.[3,4] The multicomponent synthesis have attracted considerable interest due to its automated nature and exceptional synthetic efficiency from the point of view of synthesis of new chemicals along with the term green chemistry.[5] Actually when we move through the period of evolution then its seems that, this concept is not unknown for us.

Adenine is a major constituent in basic unit in all living things i.e. nucleic acids viz.DNA and RNA was formed prebiotically by condensation of molecules of HCN in prebiotic atmosphere, under the influence of catalytic nature of NH_3.[6] Since from this event, many MCRs have been developed over the years includes Strecker synthesis,[7] Biginelli reaction[8] and Mannich reaction.[9] These MCRs are valuable because they leads to conversion of simple starting molecules to complex

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species in single step. This allow for quick approach to variant set of compounds.[10] More transformations being carried out in a single step results in less waste product (i.e. solvent) and purification time.[11] More economical protocol is resulted upon optimization of these factors.[12]

Many factors are responsible for successful journey of a multicomponent reactions; that mainly includes the appropriate starting material, temperature conditions, solvents, catalytic conditions etc.[13] Out of these, solvents plays important role throughout the chemical transformations of initial components.[14] Obviously the use of green solvents highlights the challenges on various occasion, particularly with the toxicity and environment persistence.[15] In response to these challenge, green solvents being designed for low toxicity and low biodegradability. However, any process solvent should be evaluated in terms of overall environmental impact of process.[16] It is quite eventual that if the use of a more hazardous solvents gave significant improvement to the total environmental impact of the overall process than a less hazardous alternative, then a greener choice is former.[17] The thermodynamic and kinetics of reaction carried out in green solvents are different from those in conventional molecular solvent, then the chemistry is different and unpredictable.[18] That means green solvents have many characteristic fascinating properties which make them attract fundamental interest to many chemist and thus forms the cause for their successful use in synthesis and preparation of material, catalyst, fuel cell and electrodeposition of metal.[19,20] Following points underlines the general characteristics of green solvents;[21-24] 1)Ability to dissolve a wide range of inorganic and organic compounds which is important for dissolving district combination of reagents into same phase. 2) Low or negligible vapour pressure and non-flammable. The non-flammable nature of solvents play vital role in exothermic reaction.3) Lower melting point, stability with respect to air and water. This relates with the scope of electrochemical reactions.4) High electrochemical stability and ion conductivity, it permit study of electrochemical processes that are previously beyond solvents limits and can be used instead of traditional solvent-based electrolytes.5) Thermal stability and wide liquid range .These properties of green solvents allows them to wider temperature range and tremendous kinetic control of chemical or electrochemical processes than that attained by traditional solvents. The separation techniques such as extraction, precipitation or crystallization are temperature dependent. Hence the said characteristic possesses importance in these regards too.

The use of green solvents for the synthesis of industrially important and biologically active molecules seems to be an important tool for elevating the status of synthetic organic chemistry. One of the most important chemical species in the list of novel hetero compounds is β-acetamido ketones. The novelty of this compounds reflects through their biological and pharmaceutical properties.[25,26] β-acetamido ketones serves as an important starting material in the preparation of antibiotic drug such as nikkomycin or neopolyoxines.[27,28] The ideal route for the synthesis of this class of compounds is Dakin-West reaction,[29] in which the condensation of α-amino acid with acetic anhydride in presence of base provides the α-acetamido ketones via an azalactone intermediate is explained.[30] From the review of literature it reveals that the synthetic evaluation of β-acetamido ketones under green condition, especially by using green solvents is still lacking.

Therefore, it was thought of interest for our research group to carry out an efficient multicomponent synthesis of β-acetamido ketones by using water, methanol, ethanol, perchloroethylene, xylene, toluene, and 1, 1, 1 trichloroethane as green solvents.

II. Experimental

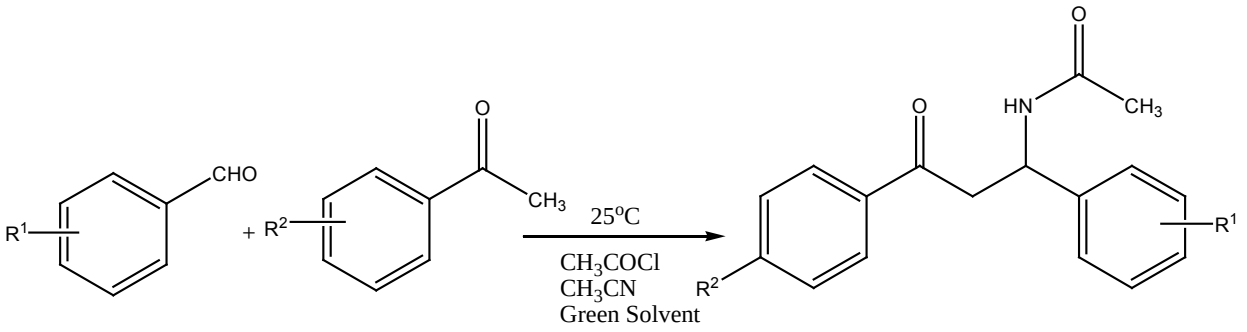
a) General

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. The melting points of all the synthesized compounds were recorded in precision digital melting point apparatus, Model MP-D and are uncorrected.

The IR spectra of the synthesized compounds were recorded on Nicolet Instruments Corporation, USA make MAGNA 550 spectrometer. The PMR spectra were recorded on Varian, USA make Mercury plus-300 MHz NMR spectrometer. The GC-MS analysis of synthesized compounds was performed on Hewlett Packard make GCD-1800A EI source analyzer at Sophisticated Analytical Instrument Facility (SAIF), IIT Bombay, Powai, Mumbai, India.

b) Typical Experimental Procedure For The Preparation of β-acetamido ketones

In typical synthesis of β-acetamido ketones, mixture of aromatic aldehyde (10 mmol), enolizable ketone (10 mmol), acetyl chloride (10 mmol) and acetonitrile (10 mmol) was well stirred (Scheme : 1) in presence of green solvents at 25° C for the appropriate time (as mentioned in Table-2). The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with ethyl acetate. Purification of product was carried out on silica gel before evaporation of solvent.



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Scheme 1 : Synthesis of β-acetamido ketones

III. Results and Discussion

In order to explore our interest for the application of Green Solvents in organic synthesis, we herein present a simple and efficient one-pot synthesis of β-acetamido ketones from enolizable ketones, aromatic aldehydes, acetonitrile and acetyl chloride in presence of green solvents viz. water, methanol, ethanol, perchloroethylene, xylene, and 1,1,1 trichloroethane at room temperature (Scheme: 1). The present protocol provide a variety of β- acetamido ketones which are obtained in good to excellent yields.(%)

In our initial endeavor, the reaction was studied with different green solvents and the best salvation activity of green solvents was optimized to room temperature and any excess of the solvent did not show further increase in terms of conversion and yield. According to this procedure, the reaction proceeded smoothly at room temperature to afford the corresponding β-acetamido ketones in good yields (Table: 2)

Table No.1 : List of β- acetamido ketone compounds synthesized by four component *reaction.

No.	Compounds	Name of compounds	M.P.(°C)
1	a	β-Acetamido-β-(phenyl) propiophenone	100-102
2	b	β-Acetamido-β-(4-methylphenyl) propiophenone	110-112
3	c	β-Acetamido-β-(3-nitrophenyl) propiophenone	114-116
4	d	β-Acetamido-β-(4-nitrophenyl) propiophenone	145-147
5	e	β-Acetamido-β-(4-chlorophenyl) propiophenone	142-144
6	f	β-Acetamido-β-(phenyl) - 4-chloropropiophenone	110-112
7	g	β-Acetamido-β-(4-chlorophenyl)-4-chloropropiophenone	138-140
8	h	β-Acetamido-β-(4-nitrophenyl)-4-chloropropiophenone	120-122
9	i	β-Acetamido-β-(phenyl)-4-methylpropiophenone	115-117
10	j	β-Acetamido-β-(Acetoxyphenyl) -propiophenone	117-119
11	k	β -Acetamido- β-(3-methoxy, 4-acetoxy-phenyl)	90-92
		propiophenone	
12	l	β -Acetamido- β-(2-methoxy)-4-nitro propiophenone	145-146
13	m	β -Acetamido- β-(2-chloro)-3-methoxy propiophenone	102-104
14	n	β -Acetamido- β-(2-chloro)-4-chloro propiophenone	167-169
15	o	β -Acetamido- β-(3-chloro)-4-nitro propiophenone	171-172
16	p	β-Acetamido-β-(2-chloro)-4-bromo propiophenone	191-192

*Reaction conditions: aromatic aldehyde=10mmol, enolizable ketone=10mmol, acetyl chloride =10mmol and acetonitrile=10mmol, green solvent (5ml), temp. = 25° C, All compounds are well characterized by spectroscopic techniques such as IR, NMR, GC-MS.

Table No.2 : *Synthetic evaluation of β-acetamido ketones

Solvent → / **Compound ↓**	water		Methanol		Ethanol		1,1,1 Trichloroethane		Perchloroethylene		Xylene	
	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)
a	62	3	86	4	78	5	85	5.5	75	5	60	6
b	65	3.5	74	2.5	75	2.5	81	3	85	6	55	5.5
c	70	4	85	3	84	3.5	80	4	71	7	80	4
d	72	4.5	65	4	86	2.5	87	2.5	95	7.5	70	5
e	60	2.5	95	3.5	80	3	75	3	86	5.2	65	5
f	55	2.5	84	5	70	4	90	4	73	4.5	75	4
g	50	4	75	4	90	3	85	3.5	78	3	65	3
h	65	2.5	78	2.5	95	5	76	4	70	5	74	2.5
i	70	5	80	3	82	6	68	3	80	4	80	3
j	69	3	84	4.5	65	3.5	84	5	90	6	65	4
k	66	8	58	9	77	6	85	10	74	5.5	68	9.5
l	85	6	94	6.5	90	10	65	8	75	7	60	5
m	90	7	80	8	72	12	71	5	68	6.5	90	6.5
n	87	7.5	80	6	75	8	77	8	65	4	90	7
o	68	4	75	6	84	5	90	6	75	8	80	4.5
p	71	6.5	78	5	80	6	70	7.5	94	10	85	9

*Reaction conditions: aromatic aldehyde=10mmol, enolizable ketone=10mmol, acetyl chloride =10mmol and acetonitrile=10mmol, green solvent (5 ml), temp.=25oC,All compounds are well characterized by spectroscopic techniques such as IR,NMR,GC-MS.

The representative data of few compounds:

1) β-acetamido-β-(2-methoxy)-4-nitro propiophenone (Table-2, Entry l):

1HNMR($CDCl_3$, 300MHz): δ2 (s, 3H), 3.55 (dd, J =6.9 and 17.5 Hz, 1H), 3.6 (dd, J = 6.5 and 17.5 Hz, 1H), 3.9(s, 3H), 5.7 (dd, J = 6.9 and 16 Hz, 1H), 6.7 (d, J = 6.9 Hz,1H), 6.9 (m, 2H), 8.1 (m, 3H), 8.3 (m, 3H); IR (KBr, cm-1)3260, 1684, 1637, 1545, 1510, 1337, 1234, 837, 742; MS(m/z,%) 344 (M+2+, 1.87), 342 (M+, 10.65), 299 (100), 150(85), 107 (25), 77 (17.8), 43 (27.6, CH_3-CO^+).

2) β-acetamido-β-(2-chloro)-3-methoxy propiophenone (Table-2,Entry m):

1HNMR($CDCl_3$, 300MHz): δ 2 (s, 3H), 3.45 (dd, J =17 and 5.7 Hz, 1H), 3.77 (dd, J = 17 and 6 Hz, 1H), 3.84 (s,3H), 5.82 (dd, J = 15 and 6 Hz, 1H), 6.93 (dbr, J = 6.7 Hz,1H), 6.9-7.5 (m, 8H). IR (KBr, cm-1) 3265, 1681, 1643,1547, 1284, 1002, 747; MS (m/z, %) 332 (M+, 3.75), 296 (83), 135 (100), 107 (49), 77 (94), 43 (73, CH_3-CO^+).

IV. Conclusions

In conclusion, we have reported an efficient procedure for the synthesis of β-acetamido ketones using green solvents. The major advantage of this method is that the ease of work-up, i.e. the products can be isolated without column chromatography. This method also offers some other merits such as clean synthesis, high yields of products, shorter reaction times and use of various substrates, which make it useful and attractive strategy for the synthesis of β-acetamido ketones.

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References References Referencias

1. Zhu, J.; Bienayme, H. Multicomponent Reactions, Wiley: Weinheim, 2005.
2. Timmons, C.; Kattuboina, A.; Banerjee, S.; Li, G. *Tetrahedron* 2006, *62*, 7151.
3. Dömling, A. Chem. Rev.2006, 106, 17–89.
4. Beck, B.; Hess, S.; Dömling, A. *Bioorg. Med. Chem. Lett.* 2000, *10*, 1701.
5. Fayol, A.; Zhu, J. *Org. Lett*. 2005, *7*, 239.
6. Leslie,E.O. *Crit. Rev. Biochemi.Mole.Bio.*2004,39, 99,123.
7. Strecker,A.*Liebigs ann.Chem.*1850,75,27.
8. Biginelli,P.*Ber.Dtsch. Chem.Ges.*1891,24,1317.
9. Mannich,C.; Kroschl,*Arch.Phar.*1912,250,647.
10. Armstrong, R. W.; Combs, A.P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem*. 1996, 29, 123–131.
11. Ramon, D. J.; Yus, M. Angew. Chem., Int. Ed. 2005, 44,1602–1634.
12. Chapman, C. J.; Frost, C. G. Synthesis 2007, 1–21.
13. Puri,S.;Kaur,B.;Parmar,A.;Kumar,H. *ISRN Organic Chemistry* 2011 1,16,211-215.
14. Shahnaz,R.;Ali,M.A.;Gholam,H.M.;Hamid,S.;Samira, E. *Synthesis* 2010,8, 1356-1360.
15. Romero, A.; Santos, A.; Tojo, J.; Rodríguez, A. *J. Haz.Mat*. 2008,1,151, 268-273.
16. Martyn, J. E.;Kenneth, R. S. *Pure Appl. Chem*. 2000 ,72, 7, 1391–1398.
17. Welton, T. *Green Chem*. 2011, 13, 225-225.
18. Singh,G.;Kumar,A.*Ind.J.Chem*. 2008,47A,495-503.
19. Seda,K.; Defne,K.T.;Ugur,A.;Oner, H. *J.Sup.Fluids* 2007 43,150–180.
20. Roger, A.S. *Green Chem*. 2005, 7, 267-278.
21. William,M.N. *ACS Symposium Series*, 2000, 767, 313–328.
22. Nelson, W. M. *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press: Oxford, 2003.
23. Maria, J.H.; Andres, R. A.; Jose, I. G.; Jose, V. S. *Chem.Eur*. J. 2010, 16, 31, 9422–9437.
24. Mieczyslaw, M. *Pure Appl. Chem*. 2000,72,7,1399–1403.
25. Casimir, J. R.; Turetta, C.; Ettouati, L.; Paris, *J. Tetrahedron Lett*. 1995, 36, 4797.
26. Godfrey, A.G.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R.; Mitchell, D. *J. Org.Chem*. 2003, *68,* 2623.
27. Dahn, U.; Hagenmaier, H.; Hohne, M.; Konig, W. A.; Wolf, G.; Zahner, H. *Arch. Microbiol*.1976, *107*, 249.
28. Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol.Chem*. 1980, *44*, 1709.
29. Dakin, H. D.; West, R. *J. Biol. Chem*. 1982, 78, 745.
30. Bhatia, B.; Reddy, M. M.; Iqbal, J. *J. Chem. Soc. Chem. Commun*. 1994, 713.

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