Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2011, 3(3): 388-392
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Microwave Assisted Robinson's Annulation: Synthesis of some novel cyclohexenones under solvent free conditions

Priya V Frank, Balakrishna Kalluraya* and Shobhitha Shetty

Department of Studies in Chemistry, Mangalore University, Mangalagangothri, Karnataka, India

---

ABSTRACT

A simple and environment friendly method for the preparation of substituted cyclohexenones by the well known Robinson's annulation technique is reported. In this method the yields are high compared to the conventional methods carried out in solvent phase. The duration of the reaction is also considerably reduced.

Key words: Cyclohexenone; microwave irradiation; Robinsons annulations.

INTRODUCTION

The use of microwave irradiation as a source of heat in synthetic chemistry offers a promising alternative to the conventional methods (1). The combination of solvent free reaction conditions and microwave irradiation leads to a large reduction in reaction times, enhancement in conversions (2), and sometimes in selectivity with several advantages of the eco-friendly approach, termed green chemistry. Microwave energy may find useful applications in chemical reactions (3-8).

Michael addition of carbon nucleophiles to electron deficient olefins is a classical and fundamental carbon-carbon bond forming reaction (9). Generally Michael additions are conducted in a suitable solvent in the presence of a strong base either at room temperature or at elevated temperatures (10). By overcoming the disadvantages like long reaction time (generally 4 to 6 hrs) tedious workup, Michael addition followed by intramolecular cyclization reaction can be carried out under eco-friendly and environmentally benign solvent free conditions.

So in this communication we report a facile synthesis of cyclohexenones by the Robinson's annulation reaction involving addition of α,β- unsaturated carbonyl compounds to active

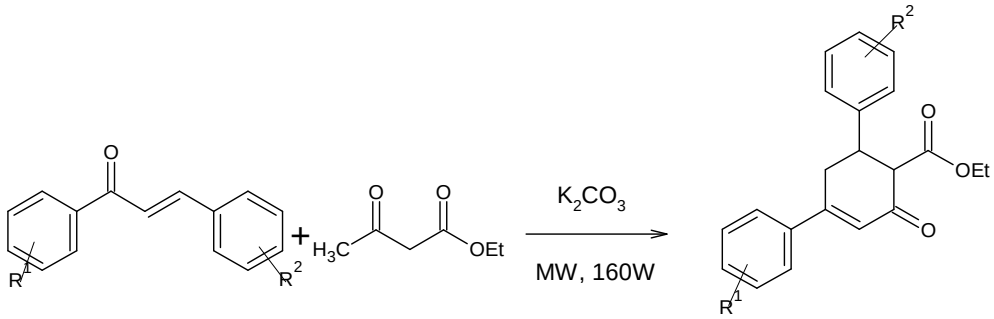
methylene compounds followed by intramolecular cyclization on the surface of potassium carbonate to afford cyclohexenones in moderate to good yields.

MATERIALS AND METHODS

All reagents were obtained commercially and were used after purification either by distillation or by recrystallization. The IR spectra were recorded on a JASCO FT IR 430 spectrophotometer in KBr pellet. The ^{1}H-NMR spectra were recorded on a Bruker AC 300F(300MHz) NMR spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra of the compounds were recorded on a Joel JMS-D300 mass spectrometer operating at 70eV. The purity of the compounds were confirmed by TLC.

Synthesis of cyclohexenones (3)

1,3-Diaryl-2-propen-1-ones (0.01mol), potassium carbonate (0.04mol) and ethylacetoacetate (0.02mol) were ground in a mortar using a pestle for uniform mixing. The paste formed was transferred to a 50mL beaker and was kept inside a microwave oven operating at 160W for 2-5 minutes. After completion of the reaction as checked by TLC, the product was poured to cold water, filtered, dried and recrystallized from ethanol-dioxane mixture. Spectral data of representative cyclohexenones are given below.



1 **2** **3**

Scheme 1

6-Carbethoxy-3-*p*-tolyl-5-*p*-chlorophenyl cyclohex-2-en-1-one (3a)

^{1}H NMR ($CDCl_3$): δ 1.07(3H,t,CH_3), δ 4.02(2H,q,CH_2), δ 2.37(3H,s,CH_3), δ 6.52(1H,s,C_2-H), δ 3.73(2H, d,d, C_4-H), δ 2.90(1H,m,C_5-H), δ 3.03(1H,d,C_6-H), δ 7.19-7.45(8H,m,Ar-H), MS: m/z 368/370.

6-Carbethoxy-3-*p*-tolyl-5-*p*-anisyl cyclohex-2-en-1-one (3b)

^{1}H NMR ($CDCl_3$): δ 1.06(3H,t,CH_3), δ 2.37(3H,s,CH_3), δ 2.91(1H, m, C_5-H), δ 3.03(1H, d, C_6-H), δ 3.68(2H, d,d, C_4-H), δ 3.79(3H, s, OCH_3), δ 4.04(2H, q, CH_2), δ 6.53(1H, s, C_2-H), δ 6.85-7.45(8H, m, Ar-H), MS: m/z 364.

6-Carbethoxy-3-*p*-anisyl-5-*p*-phenyl cyclohex-2-en-1-one (3d)
^{1}H NMR ($CDCl_3$): δ 1.03(3H,t,CH_3), δ 2.95(1H,m,C_5-H), δ 3.06(1H, d, C_6-H), δ 3.76(2H, d,d, C_4-H), δ 3.83(3H, s, OCH_3), δ 4.03(2H, q, CH_2), δ 6.52(1H, s, C_2-H), δ 6.93(2H, d, o-protons of p-anisyl), δ 7.32(5H, m, Ph), δ 7.53(2H, d, m-protons of p-anisyl) MS: m/z 350.

6-Carbethoxy-3,5-*p,p'*-dichlorophenyl cyclohex-2-en-1-one (3g)
^{1}H NMR ($CDCl_3$): δ 1.07(3H,t,CH_3), δ 2.98(1H,m,C_5-H), δ 3.05(1H, d, C_6-H), δ 3.76(2H, d,d, C_4-H), δ 3.77(3H, s, OCH_3), δ 4.04(2H, q, CH_2), δ 6.51(1H, s, C_2-H), δ 7.24-7.48(8H, m, Ar-H), MS: m/z 389/391/393.

6-Carbethoxy-3-*p*-bromophenyl-5-*p*-anisyl cyclohex-2-en-1-one (3i)
^{1}H NMR ($CDCl_3$): δ 1.06(3H,t,CH_3), δ 2.96(1H,m,C_5-H), δ 3.03(1H, d, C_6-H), δ 3.72(2H, d,d, C_4-H), δ 3.74(3H, s, OCH_3), δ 4.01(2H, q, CH_2), δ 6.50(1H, s, C_2-H), δ 7.22(2H, d, o-protons of p-bromophenyl), δ 7.37(2H, d, m-protons of p-bromophenyl), δ 7.38(2H, d, o-protons of p-anisyl), δ 7.51(2H, d, m-protons of p-anisyl).

Table 1: Characterization data of cyclohexenones (3)
Table 1

Entry	R_1	R_2	Molecular forma	Time (min)	Yield (%) MW method (conv. method)	m.p (^{0}C)	Analysis(%)Found (calculated)	
							C	H
3a	*p*-Me	*p*-Cl	$C_{12}H_{21}O_3Cl$	4	65 (58)	100	71.58(71.65)	5.77(5.7)
3b	*p*-Me	*p*-OMe	$C_{23}H_{24}O_4$	5	66 (62)	144	75.93(75.82)	6.52(6.59)
3c	*p*-Me	*p*-N(CH3)2	$C_{24}H_{27}NO_3$	5	70 (60)	136-137	76.48(76.39)	7.09(7.16)
3d	*p*-OMe	H	$C_{22}H_{22}O_4$	5	71 (62)	96-98	75.28(75.43)	6.35(6.29)
3e	*p*-OMe	*p*-Cl	$C_{22}H_{21}O_4Cl$	4	74 (59)	140	68.82(68.67)	5.40(5.46)
3f	*p*-Cl	H	$C_{21}H_{19}O_3Cl$	5	69 (58)	185-86	71.18(71.10)	5.29(5.36)
3g	*p*-Cl	*p*-Cl	$C_{21}H_{18}O_3Cl_2$	5	75 (62)	107	64.69(64.80)	4.68(4.63)
3h	*p*-Cl	*p*-OMe	$C_{22}H_{21}O_4Cl$	3	71 (61)	110-111	68.79(68.67)	5.35(5.46)
3i	*p*-Cl	*p*-N(CH3)2	$C_{23}H_{24}NO_3Cl$	3	63 (56)	104-105	69.32(69.44)	6.10(6.04)
3j	*p*-Br	H	$C_{21}H_{19}O_3Br$	5	72 (60)	204-205	63.12(63.30)	4.84(4.77)
3k	*p*-Br	*p*-Cl	$C_{21}H_{18}O_3ClBr$	5	76 (64)	95	58.26(58.15)	4.09(4.15)
3l	*p*-Br	*p*-Br	$C_{22}H_{21}O_4Br$	4	63 (55)	110-111	61.68(61.55)	4.82(4.90)

Biological Evaluation

Antimicrobial activity

The antibacterial activity of the newly synthesized cyclohexenones were carried out against four different pathogenic organisms, two each of Gram-negative and Gram-positive, they are

i. *Staphyloococcus aureus* : Gram-positive
ii. *Bacillus subtilis* : Gram-positive
iii. *Escherichia coli* : Gram-negative
iv. *Pseudomonas aeruginosa* : Gram-negative

Similarly the antifungal activity study was carried out against the fungus, *Candida albicans.* The MIC values of the newly synthesized compounds in the present investigation have been assessed by serial dilution method (11). The results of antimicrobial studies are given in **Table 2.**

Index for antibacterial and antifungal activity:
Method : Minimum inhibitory concentration by serial dilution method.
Disc size : 5.5mm
Duration : 24hr
Medium used : Peptone-water
Control : DMF
Std. for antibacterial : Furacin
Std. for antifungal : Flucanazole

Table2: Antimicrobial activity data of Cyclohexenones 3

Compd no.	Antibacterial data in MIC (µg/ml)				Antifungal activity data
	S.aureus	*P.aeruginosa*	*E.coli*	*B.subtilis*	*C.albicans*
3d	0.5	0.5	0.5	0.25	0.5
3e	0.5	0.5	1.0	0.5	1.0
3f	1.0	0.5	0.5	0.5	0.5
3h	1.0	0.5	0.5	0.5	0.5
3i	0.5	0.5	1.0	1.0	0.5
3j	0.5	0.5	0.5	0.5	1.0
Furacin(std)	0.5	0.5	0.25	0.5	-
Flucanazole (std)	-	-	-	-	0.25
Solvent Control(DMF)	-	-	-	-	-

RESULTS AND DISCUSSION

The reactions were carried out in a 500ml beaker inside a house hold microwave oven at 160W. The reactants were ground in a mortar for uniform mixing. The reactions got completed within 5 minutes in all the cases. Longer exposure and higher energy lead to decomposition of the products. The compounds were also synthesized in solvent medium by conventional method. The yields of the product obtained in solvent free microwave irradiation technique were compared with the yields obtained in the conventional solvent phase reactions. It was observed that in all such reactions carried out in solution phase, the yields were lower compared with microwave assisted solvent free method.

The propenones **1** were prepared as per the literature method by the reaction of appropriately substituted acetophenone and appropriately substituted benzaldehyde employing aqueous sodium hydroxide as the catalyst (10). These propenones **1** were mixed with ethylacetoacetate **2** in the presence of potassium carbonate and were ground in a mortar for uniform mixing (**Scheme1**) and exposed to microwave irradiation. The compounds so obtained were characterized by comparing their melting point with the samples prepared by routine solvent phase reactions and also by analytical and spectral data (**Table1**).

CONCLUSION

In conclusion we describe an microwave promoted effecient synthesis of cyclohexenones. The present procedure for the synthesis of cyclohexenones has the advantages such as it does not

involve any solvents, short reaction time, high yield compared to the conventional method. The work up procedure is also simple by the well known Robinsons annulations method.

Acknowledgement
The authors are thankful to the Head, RSIC, IIT Madras and IISc Bangalore for spectral and analytical data.

REFERENCES

[1] S.Chaddick, *Tetrahedron*., **1995**, **51**, 10403.
[2] A.Loupy, A.Retit, J.Hamelin, F.Texier-Boullet, P.Jacquault and D.Mathe, *Synthesis*., **1998,** 1213.
[3] R.S.Varma, *ACS Symposium Series No.767/ Green Chemical Synthesis and Processes*., P.T.Anastas, L.Heine and T.Williamson, American Chemical Society, Washington DC, **2000**, 292.
[4] R.S.Varma, *Green Chemistry*: *Challenging Perspectives.*, P.Tundo and P.T.Anastas., Oxford University Press, Oxford, **2000**, 221.
[5] R.S.Varma, Green Chem., **1999**, **1**, 43.
[6] R.S.Varma, *Microwaves in Organic Synthesis*., A.Loupy, Wiley-VCH, Weinheim**.,** **2002**,181.
[7] R.A.Abramovich, *Org Prep. Proc. Int.*, **1991**, **23**, 683.
[8] R.E.Gawley, Synthesis., 1976,777; M.E Jung, Tetrahedron., **1976**, **32**, 3; J.A.Peters, *Synthesis*., **1979,** 321.
[9] E.D.Bergmann, D.Ginsburg and R.pappo, Organic React., **1959**, **10**, 179.
[10] J.Rojas, N.J.Dominguez and, E.J.Charris,G.Lobo, M.Paya and L.M.Ferrandiz, Eur.J.Mwd.Chem., **2002**, **37(8)**, 699.
[11] E.J.Stokes and Ridgway, *Clinical Bacteriology*, Edward Arnold, 226 (**1980**).
[12] N.S.Rao, B.Baja, Y.K.Srivastava, *E-Journal of Chem*., **2008**, **5**, 39.
[13] E.Diez-Barra, A.de la Hoz, S.Merino and P.S.Verdu, *Tetrahedron Lett*., **38**, **2359**, 1997.
[14] S.N.Pandeya, D.Sriram, G.Nath, and E.De Clercq, *Farmaco*, **54(9)**, 624, **1999.**
[15] A.J.Pearson and R.J.Vickerman, *Tetrahedron Lett*., **39(33)**, 5931, **1998**.