ARTICLE

www.asianpubs.org

Synthesis, Characterization and Biological Evaluation of Ethyl-4'-(cyclopropane carboxamido-N-yl)-5-ary-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate

P.M. Akbari✉ and V.R. Shah

Asian Journal of Organic & Medicinal Chemistry

Volume: 4 Year: 2019
Issue: 4 Month: October–December
pp: 240–243
DOI: https://doi.org/10.14233/ajomc.2019.AJOMC-P196

Received: 25 March 2019
Accepted: 22 November 2019
Published: 31 December 2019

ABSTRACT

A series of new substituted cyclohexenone derivatives have been synthesized by the reaction of various substituted chalcones with ethylacetoacetate. Some new N-(4-(3-aryl-acryloyl)phenyl)cyclopropane carboxamide were prepared by Claisen-Schmidt condensation method in presence of sodium hydroxide in ethanol solvent under stirring. The synthesized compounds were characterized by their spectral (IR, NMR, Mass) data and screened for their antimicrobial activities against Gram-positive and Gram-negative bacteria by using standard antimicrobial drugs.

KEYWORDS

Chalcone, Cyclohexenone, Antimicrobial activity.

INTRODUCTION

The chemistry of chalcones containing an active keto-ethylenic linkage has been assumed important because of their versatility in the synthesis of many heterocyclic compounds. The growing effective literature of recent years demonstrate that chalcone being a very active intermediate through which new heterocycles with promising biological profile can be designed. Cyclohexenone and its derivatives having vast contribution in medicinal chemistry. Considerable interest has been shown in the chemistry of cyclohexenones due to their wide spectrum of therapeutic activities such as anticancer [1], anticonvulsant [2,3], antiplatelet [4], antitubercular [5], cardiovascular [6], antithrombotics [7], antibiotics [8,9], antifungal [10,11], antagonist [12], *etc*. This inspired us to synthesize ethyl-4'-(cyclopropane carboxamido-N-yl)-5-ary-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate (**2a-k**).

The structure of synthesized compounds were assigned based on elemental analysis, IR, ^{1}H NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method by measuring the zone of inhibition in mm. All the synthesized compounds have been evaluated for their antibacterial activity [13] towards Gram-positive bacterial strains such as *B. subtilis* and *S. aureus* whereas *E. coli* and *P. aeruginosa* were Gram-negative bacterial strains and antifungal activity towards *A. niger* at a concentration of 40 µg and synthesized compounds has been compared with

Author affiliations:

Department of Chemistry, Kamani Science College & Prataprai Arts College, Amreli-365601, India

✉To whom correspondence to be addressed:

E-mail: pankaj123akbari@gmail.com

Available online at: http://ajomc.asianpubs.org

standard drugs. Standard drugs like ampicillin, chloramphenicol, norfloxacin and griseofulvin were used for comparison purpose.

EXPERIMENTAL

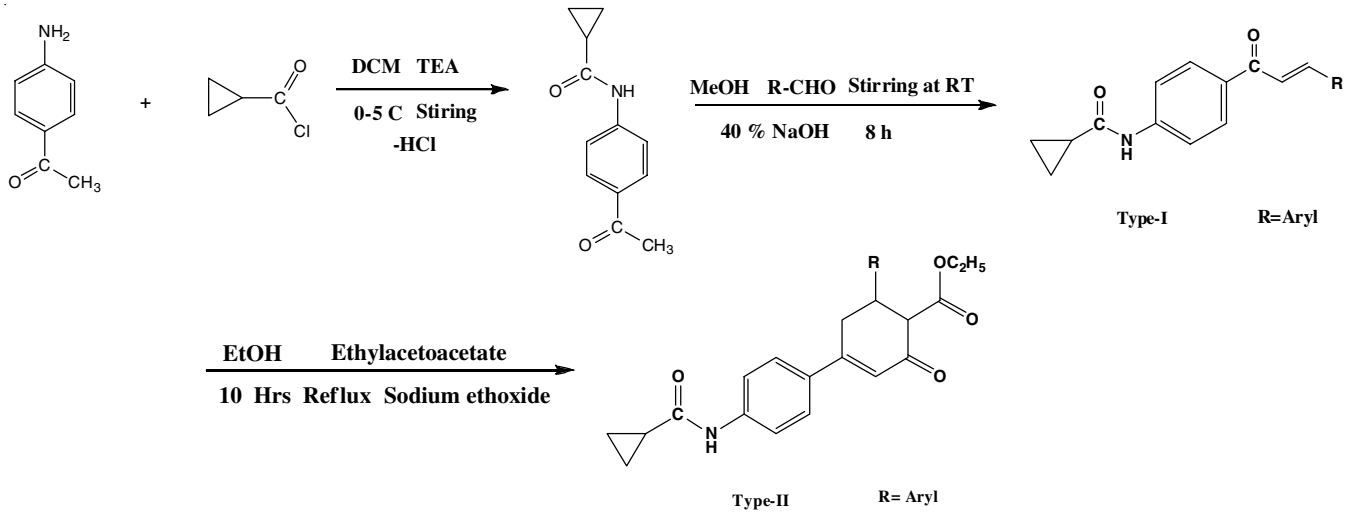
Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-435-IR spectrophotometer and ^1H NMR spectra on Bruker spectrometer (400 MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of N-(4-(3-(4-methoxyphenyl)acryloyl)phenyl)cyclopropane carboxamide (1a-k): A mixture of N-(4-acetylphenyl)cyclopropane carboxamide 0.5 g (0.01 mol) with 4-methoxy benzaldehydes 0.33 g/0.29 mL (0.01 mol) using Claisen-Schmidt condensation method in presence of 40 % NaOH using methanol as a solvent at room temperature under stirring for 8 h. Reaction was monitored by TLC. Reaction mass was poured into chilled water. Product was filtered and dried. It was recrystallized from ethanol. Yield 81.25 %, m.p.: 164 °C, Elemental analysis calculated for $C_{20}H_{19}NO_3$ Requires: C-74.75 %; H-5.96 %, N-4.36 %; O-14.94 %, Found: C-74.70 %; H-5.93; N-4.31 %; O-14.91 %.

N-(4-(3-(4-Methoxyphenyl)acryloyl)phenyl)cyclopropane carboxamide (1a-k): Yield 81.25 %, m.p.: 164 °C; IR (KBr, ν_{max}, cm^{-1}): alkane C-H str. (asym.) 2938, C-H def. (asym.) 1417, C-H o.o.p. (def) 1352, aromatic C-H str. 3040, C=C str. 1598, 1511, amine C-N str. 1294, N-H str. 3241, ether C-O-C str. 1256, ketone C=O str. 1658, vinyl CH=CH str. 3040; ^1H NMR ($CDCl_3$): δ 0.80-1.51, (m, 5H, cyclopropane), 3.748 (s, 3H, $-OCH_3$), 7.19 & 7.37 (d-d, 2H, CH=CH), 6.85-7.86 (m,8H, Ar-H), 10.48 (s, 1H, 2° amide), Mass *m/z* 322.5 (M^+); m.f.: $C_{20}H_{19}NO_3$.

General procedure for the preparation of ethyl-4'-(cyclopropane carboxamido-N-yl)-5-ary-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate (2a-k): A mixture of N-{4-[3-(4-Methoxyphenyl)acryloyl]phenyl}cyclopropane carboxamide 0.5 g (0.01 mol), ethylacetoacetate 0.4 g (0.02 mol) and sodium ethoxide 0.22 g (0.02 mol) were dissolved in ethanol. The whole reaction mass was refluxed for 10 h. The reaction mixture was poured into crushed ice and acidified with dilute HCl. Solid separated was filtered and recrystallized from ethanol. Yield 78.65 %, m.p.: 223 °C. Elemental analysis calculated for $C_{26}H_{27}NO_5$; Requires : C-72.04 %; H-6.28 %; N-3.23 %; O-18.45 %; Found : C-72.01 %; H-6.27; N-3.20 %; O-18.41 %. Similarly, other ethyl-4'-(cyclopropane carboxamido-N-yl)-5-aryl-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate were prepared (**Scheme-I**). The physical data are recorded in Table-1.

Ethyl-4'-(cyclopropane carboxamido-N-yl)-5-ary-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate (2a-k):



Scheme-I

TABLE-1
CHARACTERIZATION DATA OF THE COMPOUNDS **2a-l**

Compound No.	R	m.f.	m.w.	m.p. (°C)	Yield (%)	Nitrogen (%)	
						Found	Calcd.
2a	$-C_6H_5$	$C_{25}H_{25}NO_4$	403.47	254	74.21	3.44	3.47
2b	$-4-OCH_3-C_6H_4$	$C_{26}H_{27}NO_5$	433.50	223	78.65	3.20	3.23
2c	$-4-N(CH_3)_2C_6H_4$	$C_{27}H_{30}N_2O_4$	446.54	187	80.13	6.24	6.27
2d	$-C_4H_3O$	$C_{23}H_{23}NO_5$	393.43	184	78.54	3.55	3.56
2e	$-2-Cl-C_6H_4$	$C_{25}H_{24}ClNO_4$	437.92	155	77.12	3.18	3.20
2f	$-4-F-C_6H_4$	$C_{25}H_{24}FNO_4$	421.46	180	70.45	3.31	3.32
2g	$-4-OH-C_6H_4$	$C_{25}H_{25}NO_5$	419.47	191	72.45	3.30	3.34
2h	$-4-OH-3-OCH_3-C_6H_3$	$C_{26}H_{27}NO_6$	449.19	184	75.65	3.09	3.12
2i	$-2-OH-C_6H_4$	$C_{25}H_{25}NO_5$	419.47	188	71.45	3.32	3.34
2j	$-2-NO_2-C_6H_4$	$C_{25}H_{24}N_2O_6$	448.47	180	69.52	6.23	6.25
2k	$-4-Cl-C_6H_4$	$C_{25}H_{24}ClNO_4$	437.92	157	76.81	3.17	3.20

TABLE-2
ANTIMICROBIAL ACTIVITY

Compound No.	Zone of inhibition (mm)				
	E. coli	*B. subtilis*	*P. aeruginosa*	*S. aureus*	*A. niger*
2a	13	11	13	14	12
2b	11	16	11	13	13
2c	13	15	13	11	11
2d	13	13	14	12	12
2e	10	12	12	13	13
2f	11	12	13	12	17
2g	13	11	15	13	15
2h	14	14	13	16	12
2i	16	13	12	14	11
2j	15	15	19	15	12
2k	12	17	12	14	14
Ampicillin	17	18	19	12	0
Chloramphenicol	15	17	17	13	0
Norfloxacin	16	16	15	15	0
Griseofulvin	0	0	0	0	15

Yield 78.65 %, m.p.: 223 °C IR (KBr, ν_{max}, cm^{-1}): alkane C-H str. (asym.) 2937, aromatic C=C str. 1511, 1586, C-H i.p. (def) 1179, ester C=O str. 1738, amide C=O 1649, cyclohexenone C=O str. 1246, C=O str. 1738, ^{1}H NMR (DMSO): δ 0.81-1.80, (m, 5H, Cyclopropane), 3.73 (s, 3H, -OCH_3), 2.99-3.11 (d, 2H, cyclohexenone ring), 1.50 & 4.07 (t, q, 5H,OEt), 3.35-3.45 (m, 2H, cyclohexenone ring), 10.44 (s, 1H, 2° amide), 6.53-7.69 (m,9 H, Ar-H). Mass *m/z* 434 (M^+), m.f.: $C_{26}H_{27}NO_5$.

RESULTS AND DISCUSSION

The synthesis of N-(4-(3-aryl-acryloyl)phenyl)cyclopropane carboxamide (**1a-k**) and ethyl-4'-(cyclopropane carboxamido-N-yl)-5-ary-3-oxo-3,4,5,6-tetrahydro-biphenyl-4-carboxylate (**2a-k**) was carried out in two steps, first by the condensation of N-(4-acetylphenyl)cyclopropane carboxamide) with different aromatic aldehydes by Claisen-Schmidt condensation in presence base catalyst to give chalcone derivatives (**1a-k**), which in next step were refluxed with ethylacetoacetate to yield cyclohexenone derivatives [(Type-II) (**Scheme-I**)]. The formulae of the selected compounds were confirmed by the Elemental analysis and their structures were determined by IR, ^{1}H NMR and mass spectral data.

Antibacterial activity: It has been observed from the microbiological data (Table-2) that all compounds **1a-k** and **2a-k** were found to be mild to moderately active against Gram-positive and Gram-negative bacterial strains.

Antifungal activity: The antifungal data (Table-2) revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds against *A. niger*. The antibacterial activity was compared with standard drug *viz*. ampicillin, chloramphenicol, norfloxacin and antifungal activity was compared with standard drug *viz*. griseofulvin.

Conclusion

The current study leads to a convenient synthetic method for the synthesis of new compounds which show significant antibacterial and antifungal activities. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

ACKNOWLEDGEMENTS

The authors are very much grateful to authorities of Kamani Science College, Amreli for providing research facilities & Principal and Management of Shree M. & N. Virani Science College, Rajkot for providing Spectral data of IR and MASS and also thankful to Department of Chemistry Saurashtra University Rajkot for IR, NMR, Mass Spectral & Elemental analysis. The authors are thankful to Pramukh Swami Science College, Kadi for providing Antimicrobial activities data.

REFERENCES

1. M. Das and K. Manna, Bioactive Cyclohexenones: A Mini Review, *Curr. Bioactive Comp.*, **11**, 239 (2015); https://doi.org/10.2174/1573407211041512301041 38.
2. K.R. Scott, I.O. Edafiogho, E.L. Richardson, V.A. Farrar, J.A. Moore, E.I. Tietz, C.N. Hinko, H. Chang, A. El-Assadi and J.M. Nicholson, Synthesis and Anticonvulsant Activity of Enaminones. 2. Further Structure-Activity Correlations, *J. Med. Chem.*, **36**, 1947 (1993); https://doi.org/10.1021/jm00066a003.
3. J.E. Foster, J.M. Nicholson, R. Butcher, J.P. Stables, I.O. Edafiogho, A.M. Goodwin, M.C. Henson, C.A. Smith and K.R. Scott, Synthesis, Characterization and Anticonvulsant Activity of Enaminones. Part 6: Synthesis of Substituted Vinylic Benzamides as Potential Anticonvulsants, *Bioorg. Med. Chem.*, **7**, 2415 (1999); https://doi.org/10.1016/S0968-0896(99)00185-6.
4. D.P.G. Hamon, P.J. Hayball, R.A. Massy-Westropp, J.L. Newton and J.G. Tamblyn, Enantioselective Synthesis of the Four Isomers of the Biologically Active Metabolite of the 2-arylpropanoic Acid NSAID, Ximoprofen and Assessment of their Inhibitory Activity on Human Platelet Cyclooxygenase *in vitro*, *Tetrahedron*, **7**, 263 (1996); https://doi.org/10.1016/0957-4166(95)00443-2.
5. D.H. Vyas, S.D. Tala, J.D. Akbari, M.F. Dhaduk and H.S. Joshi, Synthesis, Antimicrobial and Antitubercular Activity of Some Cyclohexenone and Indazole Derivatives, *Indian J. Chem*., **48B**, 1405 (2009).
6. S. Liu, W. Wen, W. Zou, M. Guo, J. Zhang, J. Huang, Y. Li and J. Huo, Cyclohexenone Extract of *Antrodia camphorata*, Chinese Patent CN20071004235 (2007).
7. Y. Arai, S. Kawanami and Toru Koizumi. Novel Route to Some Biologically Important Compounds Starting with a Common Chiral, Bicyclic, Fused Lactone: Enantioselective Synthesis of (–)-Boschnialactone and Two Antithrombotics, *J. Chem. Soc., Perkin Trans*. 1, 28, 2969 (1991); https://doi.org/10.1039/P19910002969.
8. S.M. Roberts and G.M. Santoro, Cyclohexenone and Cyclohexanone Derivatives, European Patent EP2064170A2 (2006).

9. M.I. El-Zahara, S.S. Abd El-Karim, M.M. Anwar and E.M. Danial, Synthesis, Antimicrobial and Antioxidant Activities of Some Novel Cyclized Naphthyl Cyclohexanone Derivatives, *Der Pharma Chem.*, **2**, 118 (2010).
10. A.M. Ghatole, K.R. Lanjewar, M.K. Gaidhane and K.M. Hatzade, Evaluation of Substituted Methyl Cyclohexanone Hybrids for Anti-tubercular, Anti-bacterial and Anti-fungal Activity: Facile Syntheses Under Catalysis by Ionic Liquids, *Spectrochim. Acta A: Mol. Biomol. Spectrosc*., **151**, 515 (2015); https://doi.org/10.1016/j.saa.2015.06.035.
11. J.Y. Li, J.K. Harper, D.M. Grant, B.O. Tombe, B. Bashyal, W.M. Hess and G.A. Strobel, Ambuic Acid, A Highly Functionalized Cyclohexenone with Antifungal Activity from *Pestalotiopsis* spp. and *Monochaetia* sp., *Phytochemistry*, **56**, 463 (2001); https://doi.org/10.1016/S0031-9422(00)00408-8.
12. P.J. Harrison, Preparation of a Cyclohexanone Intermediate for Synthesis of Thromboxane Antagonists, *Tetrahedron Lett*., **30**, 7125 (1989); https://doi.org/10.1016/S0040-4039(01)93441-0.
13. A.L. Barry, The Antimicrobial Susceptibility Test: Principle and Practices, edited by llluslea & Febiger: Philadelphia, USA, p. 180 (1977).