ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 7, Issue, 12, pp. 14549-14553, December, 2016

International Journal of Recent Scientific Research

Research Article

SYNTHESIS OF SUBSTITUTED β-DIKETONES AND STUDY OF THEIR ANTIBACTERIAL ACTIVITY

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ARTICLE INFO

Article History:

Received 15th September, 2016
Received in revised form 25th October, 2016
Accepted 23rd November, 2016
Published online 28th December, 2016

Key Words:

β diketones, antibacterial activity

ABSTRACT

Some new substituted β-Diketones were synthesised by using 2-hydroxy acetophenones and different benzoic acids. These newly synthesised β-Diketones were characterised by IR and NMR spectra. β-Diketones were then screened for antibacterial activity against S.aureus, E. Coli and S.typhi.

INTRODUCTION

β-Diketones compounds, whose simplest and the most widely known member is pentane-2,4-dione (informally referred to as acetylacetone), have a number of very interesting and specific properties due to their structure (the presence of two carbonyl groups separated with one carbon atom). Their crucial feature is keto-enol tautomerism, the presence of the ketone and the enol forms in equilibrium. Due to the presence of two carbonyl groups, β-Diketones are valuable substrates in many chemical synthesis.

1, 3-Diketones are one of the most synthetically important classes of compounds. Various drugs containing the heterocyclic moieties, such as pyrazole, isoxazole, carbazole, imidazole and thaizole etc. are the proven drugs against various ailments and are synthesized via a diketone. The research being stimulated by the versatility of these compounds as their biological activities as evidenced from their anticancer1, anti-tumor2, anti-oxidant3, anti-inflammatory4, anti-viral5 and immunomodulatory activities6.

MATERIALS AND METHODS

All the laboratory chemicals and solvents required for the study were of highest purity commercially available. Melting points of all synthesised compounds were determined by melting point apparatus. The purity of synthesised compounds was checked by thin layer chromatography on silica –G layers. IR spectra were recorded on FTIR spectrophotometer using KBR pallets. NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer.

Synthesis of substituted β-Diketones

The synthesis involves following steps:

Preparation of 5-chloro-2-hydroxy-4-methyl acetophenone(1):

p-chloro-m-cresyl acetate was prepared by acetylation of p-chloro-m-cresol.

Then prepared p-chloro-m-cresyl acetate (50ml) and anhydrous aluminium chloride (120 g) were heated at 120^0c for 60 min. in an oil bath. The reaction mixture was cooled and decomposed with ice-cold water containing a little HCl (10%) to get Ketone.

Preparation of 2-benzoyloxy acetophenones (2a,b,c)

5-chloro-2-hydroxy-4-methyl acetophenone (1) (0.04 mol) and aromatic carboxylic acid (0.05 mol) were dissolved in pyridine and $pocl_3$ is added drop by drop with constant stirring till the viscous mass is obtained. Maintain the temperature below 10^0c during the addition of $pocl_3$ to the reaction mixture. The reaction mixture is allowed to stand for overnight at room temperature .The reaction mixture is decomposed by 10% HCl. The product thus separated was filtered, washed with water followed by sodium bicarbonate (10% solution) and then again washed with water. The solid product was crystallised from ethanol to obtained corresponding 2-benzoyloxy acetophenones.

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5-chloro-2-(4' chloro benzoyloxy)-4-methyl acetophenone (2a) was prepared by above method by using 4-chloro benzoic acid. 5 chloro-2-(2'-4'dichloro benzoyloxy) -4-methyl acetophenone (2b) was prepared by using 2-4 dichloro benzoic acid. Similarly 5 chloro -2-(4' methoxy benzoyloxy) -4-methyl acetophenone (2c) was prepared by using p-methoxy benzoic acid.

Preparation of 1-(2'-hydroxy aryl)-3-aryl propane1,3-diones (3 a,b,c)

2-substituted benzoyloxy acetophenones (2a-b) (0.05 mol) was dissolved in dry pyridine (40 ml). The solution was warmed up to about 60^0c and pulverised KOH (0.15 mol) was added slowly with constant stirring. After four hours the reaction mixture was acidified by adding ice cold dilute HCl (1:1). The solid product thus separated was filtered, washed with sodium bicarbonate solution (10%) and finally with water. It is then crystallised from ethanol acetic acid mixture to get 1-(2'-hydroxy aryl)-3-aryl propan-1-3- diones (3 a,b,c).

Spectral data of substituted β-Diketones

Spectral data of 3a:

IR: 3424 cm^{-1} (Phenolic -OH stretch), 3093 cm^{-1} (Aromtic C-H srretch), 1685 cm^{-1}(C=O stretch), 1611 cm^{-1} (Aromatic C=C stretch), 2927 cm^{-1}(C-H stretch of methyl group), 761 cm^{-1}(Aromatic substitution C-Cl), H NMR: δ 3.54 (S, 1H of OH), δ 2.49 (S, 3H of CH_3), δ 2.61 (S, 2H of CH_2), δ 6.8-8.1 (m,6H of Ar-H), δ 11.94 (tautomerism).

Spectral data of 3b:

IR: 3444 cm^{-1} (Phenolic -OH stretch), 3095 cm^{-1} (Aromtic C-H srretch), 1749 cm^{-1}(C=O stretch), 1610 cm^{-1} (Aromatic C=C stretch), 2924 cm^{-1}(C-H stretch of methyl group), 734 cm^{-1}(Aromatic substitution C-Cl), H NMR: δ 4.52 (S, 1H of OH), δ 2.37 (S, 3H of CH_3), δ 2.52 (S, 2H of CH_2), δ 6.6-8.1 (m,5H of Ar-H), δ 11.8 (tautomerism).

Spectral data of 3c:

IR: 3470 cm^{-1} (Phenolic -OH stretch), 3005 cm^{-1} (Aromtic C-H srretch), 1686 cm^{-1}(C=O stretch), 1605 cm^{-1} (Aromatic C=C stretch), 2939 cm^{-1}(C-H stretch of methyl group), 794 cm^{-1}(Aromatic substitution C-Cl), H NMR: δ 4.68 (S, 1H of OH), δ 2.44 (S, 3H of CH_3), δ 3.80 (S, 2H of CH_2), δ 3.89(S,3H of O CH_3), δ 6.8-8.0 (m,6H of Ar-H), δ 11.56 (tautomerism).

Table 1 Physical data of β-diketones

Sr. No.	Compound	M.F	M.P °c	colour	%Yield
1	3a	$C_{16}H_{12}Cl_2O_3$	162-164	Yellow	72
2	3b	$C_{16}H_{11}Cl_3O_3$	125-126	Yellow	69
3	3c	$C_{17}H_{15}ClO_4$	142-144	Yellow	57

Antibacterial activity

All the synthesised β-diketone were screened for their antibacterial activity against S. Aureus, E. Coli and S. typhi at 1000mg/l using ciprofloxacin as a standard drug. Agar diffusion method was employed to study the activity. Initially, the stock culture of bacteria were revived by inoculating on broth media and grown at 37^0c for 18 hrs. The agar plates of the above media were prepared and wells were made in the plate.

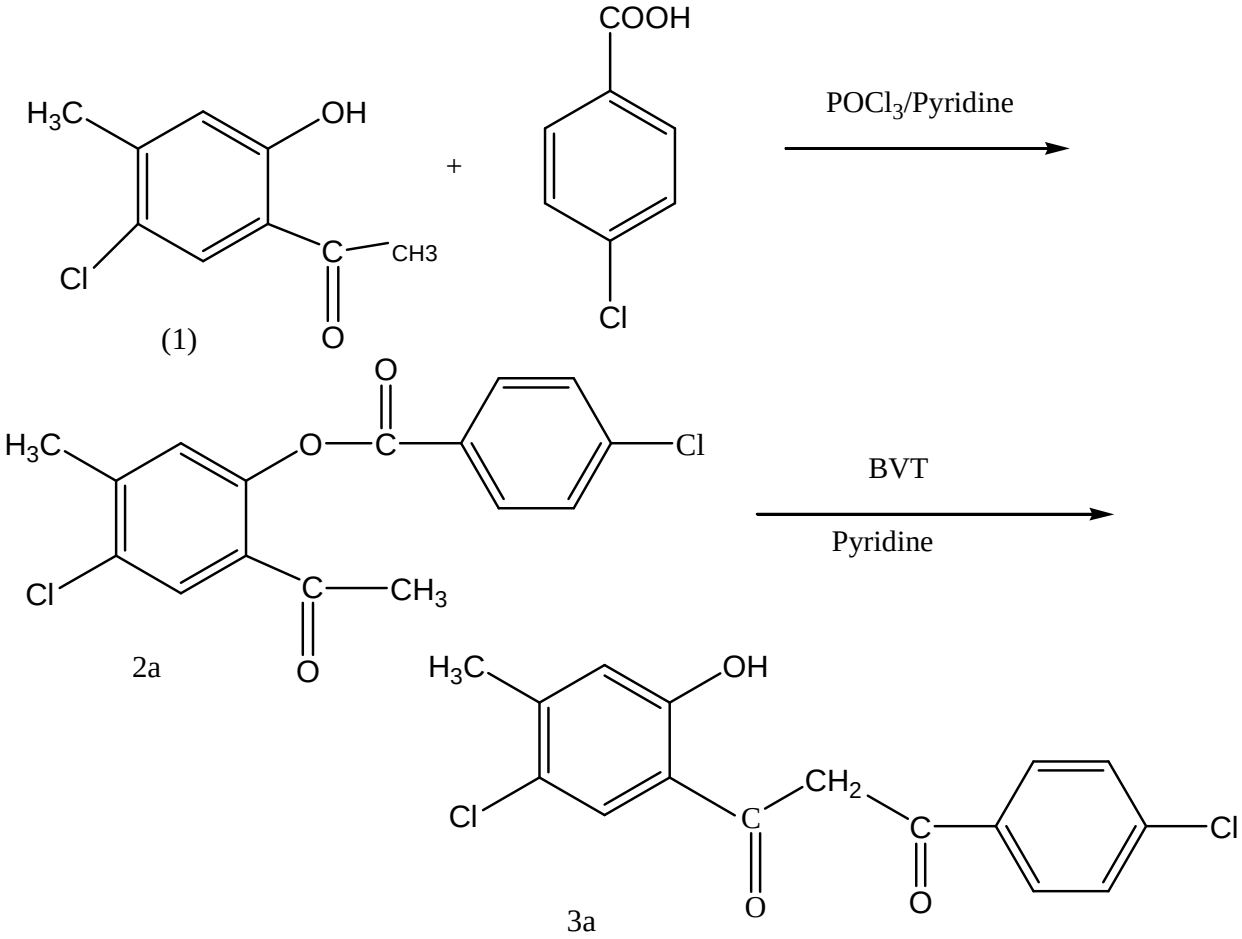

Fig.1 Experimental scheme for the synthesis of 1 -(2'hydroxy-4'methyl-5' chloro phenyl)-3(4' chloro phenyl) propane 1-3-dione (3a)

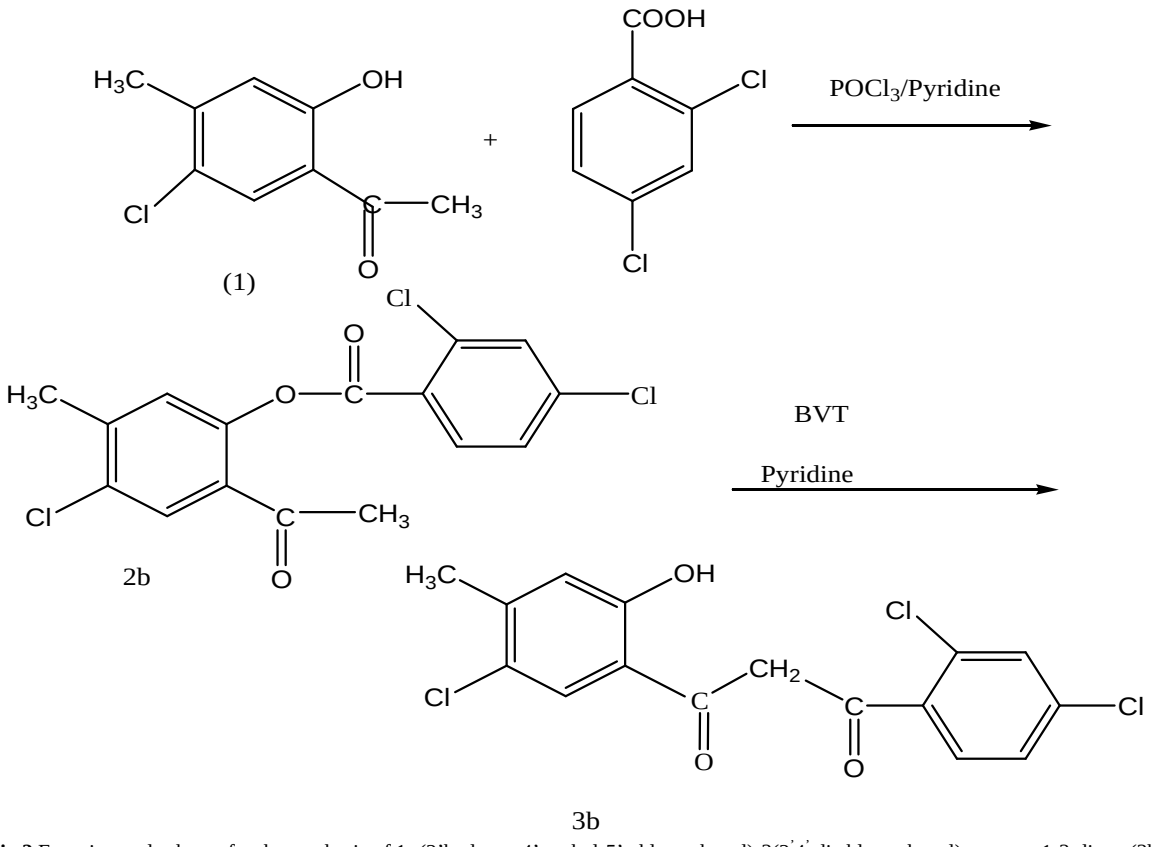

Fig.2 Experimental scheme for the synthesis of 1 -(2'hydroxy-4'methyl-5' chloro phenyl)-3(2'4' di chloro phenyl) propane 1-3-dione (3b)

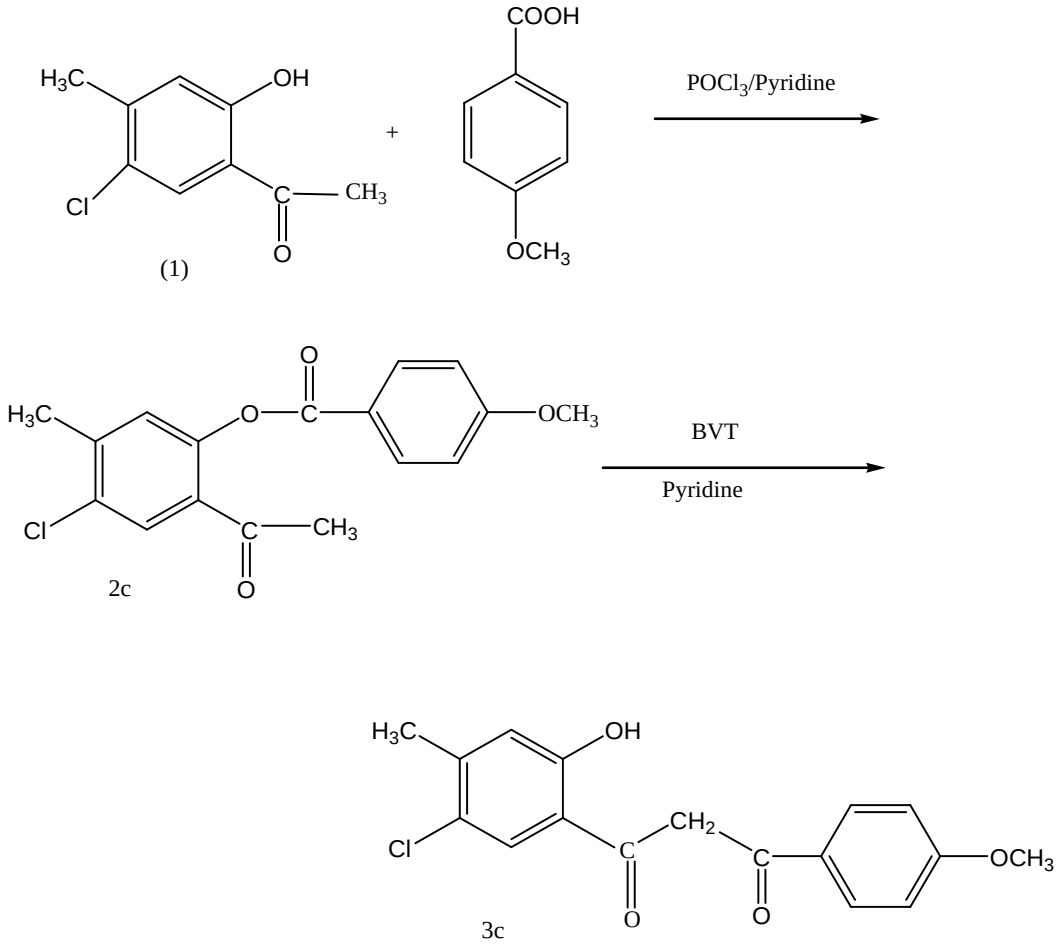

Fig.3 Experimental scheme for the synthesis of 1 -(2'hydroxy-4'methyl-5' chloro phenyl)-3(4' methoxy phenyl) propane 1-3-dione (3c)

Each plate was inoculated with 18 hr. old culture and spread evenly on the plate. After 20 min, the wells were filled with the compound and antibiotic at different concentrations. All the plates were incubated at 37^0c for 24 hr. and the diameter of inhibition zone were noted.

Table-2 Antibacterial activity of synthesised β-Diketones 3a-c

Sr. NO.	Compounds	Antibacterial activity inhibition zone (mm)		
		S.aureus	E.coli	S.typhi
1	3a	6	4	3
2	3b	5	7	2
3	3c	5	1	2

RESULT AND DISCUSSION

In this work, total three substituted β-Diketones namely 3a-c are synthesised from different benzoic acids by Baker Vankatraman rearrangement. All the synthesised β-diketone were screened for their antibacterial activity against S. Aureus, E. Coli and S. Typhi. From the data on Antibacterial activities given in table, it was observed that, compound 3a showed moderate activity against S.aureus while week activity against E. Coli and S. Typhi. Compound 3b showed moderate activity against E. Coli and week activity against S. Aureus and S.Typhi.

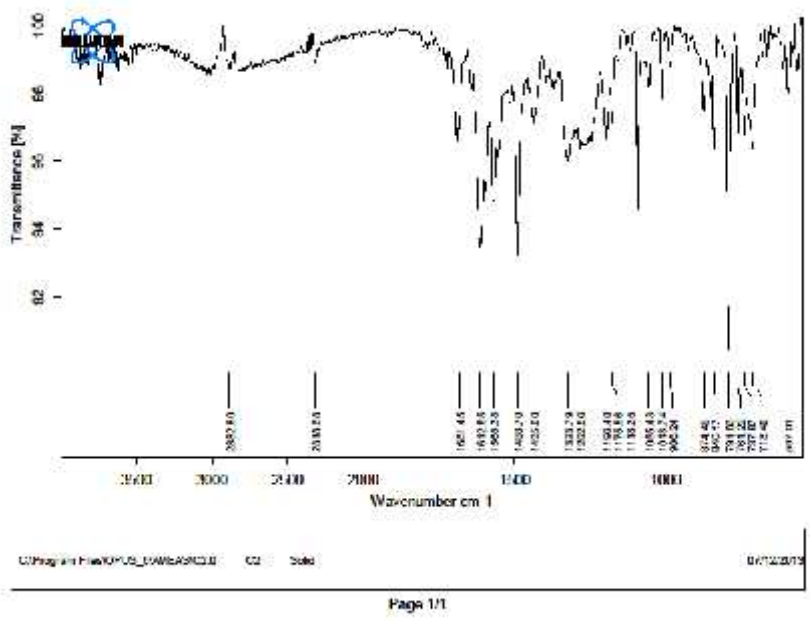

Fig 4 IR spectra of 1 -(2'hydroxy-4'methyl-5' chloro phenyl)-3(4' chloro phenyl) propane 1-3- dione (3a)

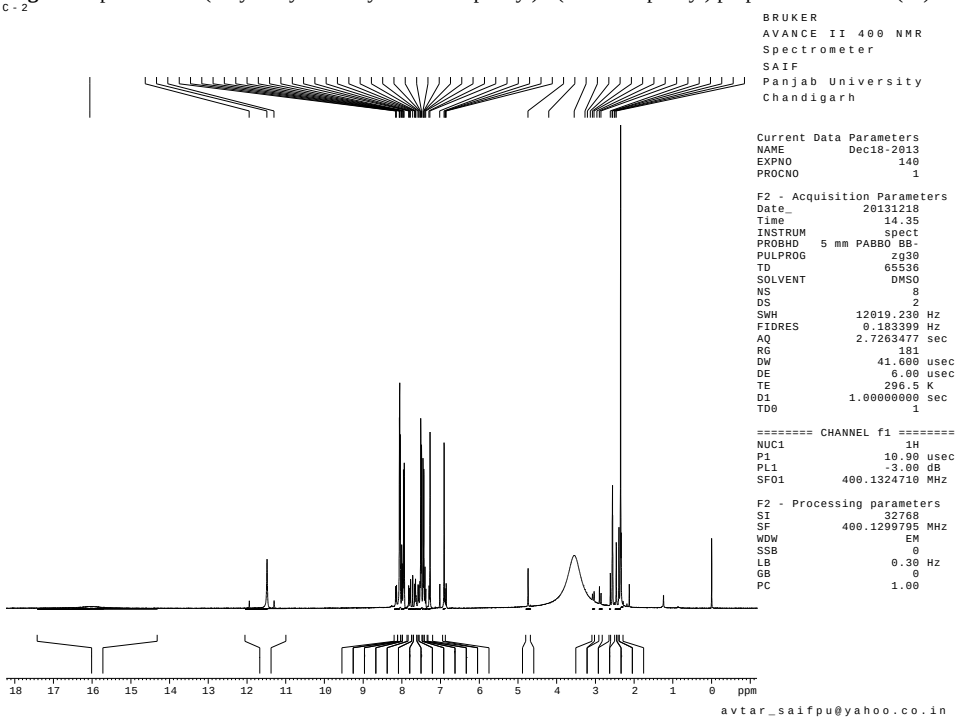

Fig 4 ^{1}HNMR spectra of 1 -(2'hydroxy-4'methyl-5' chloro phenyl)-3(4' chloro phenyl) propane 1-3- dione (3a)

And compound 3c showed comparatively week activity against all the three bacteria. The probable correlation between structure and activity can be established, that the presence of halogen in the moiety increases toxicity towards bacteria.

CONCLUSION

Antibacterial activity against all the three bacteria is concerned substituted β-Diketone 3a can be used as lead compound as it showed moderate antibacterial activity against all the three bacteria tested.

Acknowledgement

Authors are thankful to principal, Vidyabharati Mahavidyalaya, Amravati for providing laboratory facilities, Biogenics. Research and training centre in Biotechnology, Hubli, Karnataka. And SAIF Punjab university for their support.

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How to cite this article:

Jayashri N. Angaitkar and Bodkhe P. S.2016, Synthesis of Substituted β-Diketones and Study of Their Antibacterial Activity. *Int J Recent Sci Res.* 7(12), pp. 14549-14553.