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Synthesis of Novel Butyl Paraben Hybrid Derivative

Pradip S. Shelar[1], Vijay D. Gangan[2*], Snehal D. Patel[2], Tanuja P. Parulekar[3], Sharad G. Shilkande[4], Mahendra H. Janrao[5], Saurabh Balasaheb Patil[6], Yogesh S. Shelar[7], Dipali G. Wavhal[7]

[1]Department of Chemistry, K. J. Somaiya college of Arts, Science and Commerce, Mohinirajnagar, Kopargaon - 423601, Dist. Ahemadnagar, Maharashtra, India

[2]Department of Chemistry, Reena Mehta College of Arts, Commerce, Science and Management Studies, Bhayandar (W), Thane – 401101, Maharashtra, India

[3]Department of Chemistry, S.I.W.S. N.R. Swamy College of Commerce & Economics and Smt. Thirumalai College of Science, Wadala, Mumbai-400031, Maharashtra, India

[4]Department of Chemistry, Sheth J. N. Paliwala College of Arts, Science and Commerce, Pali-Sudhagad, Dist. Raigad – 410205, Maharashtra, India

[5]Department of Chemistry, VPMK's Art, Commerce and Science College Kinhavali, Taluka Shahapur, Dist. Thane 421403, Maharashtra, India

[6]MVPs KKW Arts, Science and Commerce College, Pimpalgaon (B), Nashik, Maharashtra, India

[7]SICES Degree College Of Arts, Science and Commerce College, Jambhul Phata, Ambernath-Badlapur Road, Ambernath (West) 421505, Maharashtra, India

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ABSTRACT

Parabens are class of chemicals widely used as preservatives in the cosmetic and pharmaceutical industries. They are effective preservatives in many types of formulas. These compounds and their salts are used primarily for their bacterial and fungicidal properties. They are also used as food additives. Their analogues viz. ethers, esters and hybrid / fused molecules also possess various biological activities which prompted us to synthesize few more analogues for their future application as bioactive molecules. The synthesized compound was unambiguously characterized by IR, 1HNMR, Maas and elemental analysis.

Keywords : parabens, IR, 1HNMR, Mass, elemental analysis and hybrid molecule etc.

I. INTRODUCTION

Phenolic phytochemicals are known to exhibit anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antiatherosclerosis and immunomodulatory activities in animals[1,2]. These are mostly polyphenols known as secondary plant metabolites[3] present in plant and trees. One of such compound is 4-hydroxy benzoic acid which is used as antifungal, antimutagenic, antisickling, esterogenic[4]

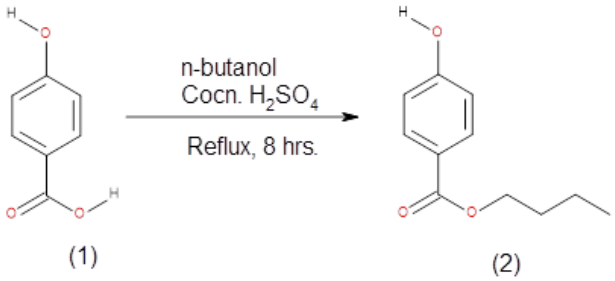
and antimicrobial[5] agent. It is primarily known as the basis for the preparation of its esters, known as parabens, which are used as preservatives in cosmetics. Parabens are used for their bactericidal and fungicidal properties. They can be found in shampoos, commercial moisturizers, shaving gels, personal lubricants, topical / parenteral pharmaceuticals, spray tanning solution, makeup and toothpaste. They are also used as food additives. In the present study, we are converting 4-hydroxy benzoic acid to butyl paraben using conventional method and their further diversification to ester derivative. It is an antimicrobial preservative used in many cosmetics, as a food flavoring agent and as a suspending agent for medications. Since butyl paraben is naturally occurring active compound having antioxidant and antimicrobial properties, we decided to make a library of compounds[6,7] using various permutation and combinations to come up with novel ether, ester and hybrid derivatives of butyl paraben using conventional methods. The objective of this study is to condense two molecules of the same disease domain to produce more potent candidate in the same disease domain or to condense two molecules of different disease domain to produce mixed variety of those disease domain or to have drug candidate with entirely different biological activity. In the present work, we are converting 4-hydroxy benzoic acid to butyl paraben which in turn further converted to its hybrid derivative using conventional method.

II. RESULTS AND DISCUSSION

Preparation of Butyl Paraben :- It was prepared by refluxing 4–hydroxy benzoic acid (25 gms) with n-butanol (250 ml) using sulphuric acid (1 ml) as a catalyst for 8 hrs. The progress of the reaction was monitored by TLC for the completion of reaction.

Work up :- The reaction mixture concentrated under reduced pressure to minimum and to that 200 ml of dichloromethane + 200 ml of water was added. The aqueous layer was extracted successively with dichloromethane (2 x 100 ml). The total organic layer was washed with water (200 ml), brine (100 ml) and concentrated to yield butyl paraben quantitatively (33.75 gms, 96 %).

Reaction Scheme :



(1) 4-hydroxybenzoic acid

(2) butyl 4-hydroxybenzoate

The above procedure can be scaled up to get more quantities of butyl paraben.

Butyl-4-hydroxybenzoate (1)

^{1}H NMR (500 MHz, $CDCl_3$) δppm : 0.985 (t, J = 7.5 Hz, 3H, terminal –CH_3 from butyl paraben moiety), 1.4 – 1.6 (m, 1 x –CH_2, 2H, -CH_2 from butyl paraben moiety), 1.7 – 1.8 (m, 1 x –CH_2, 2H, -CH_2 from butyl paraben moiety), 6.41 (brs, 1H, -OH, D_2O exchangeable), 7.256 (d, J = 9.0 Hz, 2H, ortho coupling, ArH from butyl paraben moiety), 8.105 (d, J = 9.0 Hz, 2H, ortho coupling, ArH from butyl paraben moiety); TOF MS ES : 195 (M + H), 217 (M + Na); Molecular formula $C_{11}H_{14}O_3$; Colourless, odorless crystalline powder (26.4 gms, 96.0 %). Melting range 68 – 69^0 C; Anal. Calcd. For $C_{11}H_{14}O_3$: C 68.0 % H 7.30 % O 24.70 %. Found : C 67.98 % H 7.28 % O 24.72 %;

Butyl paraben was then subsequently converted to its hybrid derivative as mentioned below.

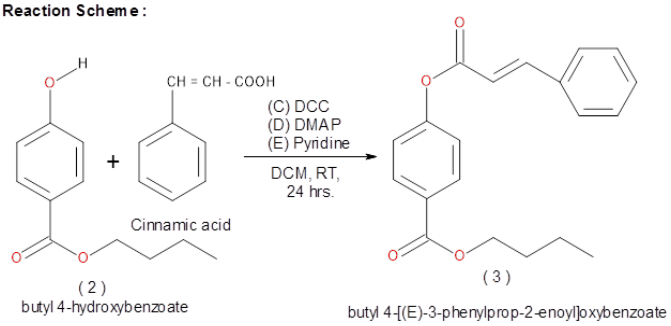
Diversification of butyl paraben to its hybrid derivative (3) :- This was prepared by following general method as depicted below.

To a stirred solution of [A] (1 eq.) in 40 ml dichloromethane was added [C] (1.4 eq.), [D] (0.05 eq.), [E] (0.5 eq.) and stir the reaction mixture at room temperature for 5 min. Clear solution of reaction mixture was obtained. To this, compound [B] (1.4 eq.) was added and stirring continued at room temperature for next 8 hr. As the reaction proceeds, urea derivative precipitates out as by product. The progress of the

reaction is monitored by TLC for the completion of reaction.

Work up :- The reaction mixture filtered through Buchner funnel, wash the cake with 10 ml of dichloromethane. This get rid of byproduct urea derivative. The total organic layer was concentrated to minimum, preadsorbed on silica gel (100 – 200 mesh) and purified by column chromatography with increase in concentration of ethyl acetate in petroleum ether. The general yields of these reactions ranges between 70 – 80 %.

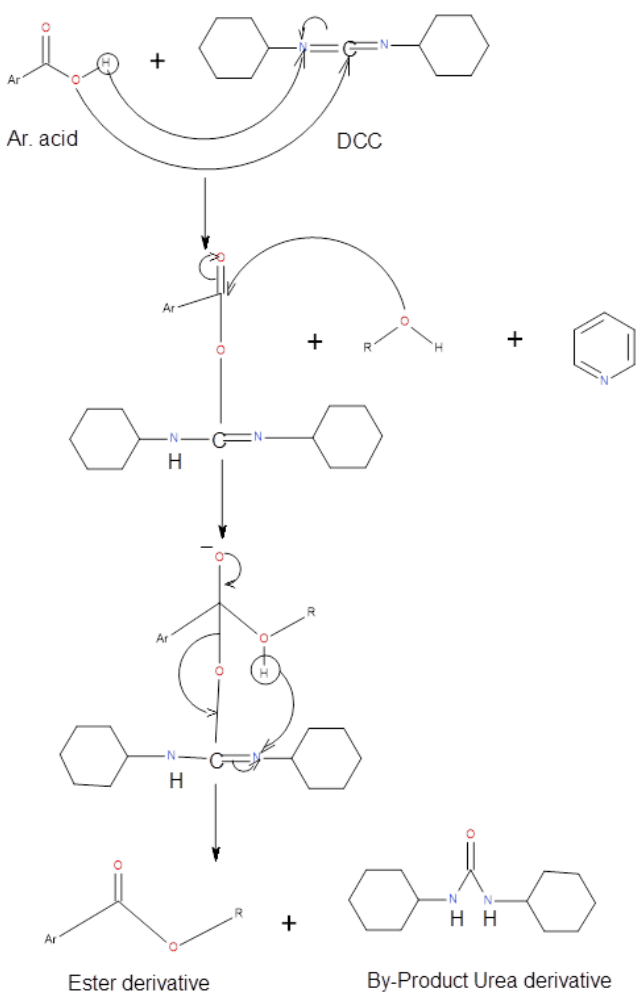
Reaction Scheme :



Compound No.	IUPAC Name
3	Butyl-4-[(E)-3-phenylprop-2-enoyl]oxybenzoate

The general mechanism for this reaction can be given as follows.

Probable mechanism for fused / hybrid molecules :



Butyl-4-[(E)-3-phenylprop-2-enoyl]oxybenzoate (3)

^{1}H NMR(CDCl$_3$, 500 MHz) δ ppm :- 0.985 (t, *J* = 7.5 Hz, 3H, terminal –CH$_3$ from butyl paraben moiety), 1.4 – 1.6 (m, 1 x –CH$_2$, 2H, -CH$_2$ from butyl paraben moiety), 1.7 – 1.8 (m, 1 x –CH$_2$, 2H, -CH$_2$ from butyl paraben moiety), 4.331 (t, *J* = 6.0 Hz, 2H, -OCH$_2$ from butyl paraben moiety), 7.303 (dd, *J* = 9.0 Hz, 2.0 Hz, 2H, ArH, ortho as well as meta coupling from butyl paraben moiety), 6.629 (d, *J* = 16.0 Hz, 1H, trans double bond from cinnamic acid moiety), 7.89 (d, *J* = 16.5 Hz, 1H, trans double bond from cinnamic acid moiety), 7.2 – 8.2 (m, 9H, ArH from Cinnamic acid and butyl paraben moiety); TOF MS ES : 325 (M + H), 347 (M + Na); Molecular Formula C$_{20}$H$_{20}$O$_4$; Off white solid (1.30 g, 78 %); Melting range 108 – 110^{0}C;

Elemental Analysis, Calcd : C 74. 10 % H 6.22 % O 19.71 % Found C 74.08 % H 6.19 % O 19.73 %;

The most significant features of this methodology are (a) good accessibility of the reagent and its stability (b) a stoichiometric amount of reagent can be used by direct weighing, avoiding excess (c) no evolution of hazardous vapours during the reaction (d) the total elimination of the use of toxic organic solvents (e) a simple experimental procedure (g) good control over the outcome of the reaction by varying the amount of reagent (h) less expensive and (i) very simple reaction work up with avoidance of by-product. The aforesaid protocol thus provides an improved procedure for the synthesis of useful hybrid derivatives having important pharmaceutical, agricultural and other physicochemical properties.

III. EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus using digital thermometer. IR spectra were recorded on a Shimadzu FTIR Prestige model as KBr pellet. ^{1}H NMR spectra were recorded on a Varian 500 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million down field from tetramethyl silane. Mass spectra were recorded on a TOF MS ES mass spectrometer. Elemental analysis were carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

IV. CHROMATOGRAPHIC SYSTEM

Column chromatography : For column chromatography 100 – 200 mesh Acme grade silica gel is used. The crude reaction mixture is concentrated under reduced pressure to yield crude mass which is preadsorbed on silica gel and purified by column chromatography with increase in concentration of Ethyl acetate in Petroleum ether. The fractions having similar ‘rf” values were pooled together, concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography : TLC plates were prepared using silica gel G (ACME, BOMBAY). Pet. ether: EtOAc (85 : 15) was used as the solvent system.

Radial chromatography : The circular glass plates of thickness 1 mm, were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed.

V. CONCLUSION

The novel ester derivative of butyl paraben was synthesized by cost effective industry viable process following the principle of green chemistry. The synthesis of ester derivative is achieved using DCC as dehydrating agent in a reasonably good yield. The probable mechanism for the formation of ester derivative was also discussed.

In depth analysis of these compounds through structure activity relationship studies would provide further insight and can be an interesting topic of future studies.

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