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Synthesis and Anti Bacterial Activities of Novel Phthalide Derivatives

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Abstract

Phthalides are a diverse group of metabolites produced by wide range of organisms from plants to fungi. Phthalides have many different biological activities. They can function as antibacterials, muscle relaxants, antivirals, effect cardiac functions and more. Significant effort has been focused on synthesizing phthalides, but most asymmetric methods require chiral auxiliaries or chiral organometallics, few are catalytic, and none is atom-economical. This work reports novel bioactive phthalides and its synthesis.

Introduction

Over the years, several hundreds of compounds with antibiotic activity[1]have had been isolated from microorganisms. Traditional drug discovery[2] began with a known pathological phenomenon in an organism and the development of a therapeutic theory to combat this process. Pharmaceutical industries were succeeding in producing antimicrobial drugs to combat disease producers with single resistant determinants. During the early 1980's most of the bacterial infections were considered won, but now antimicrobial resistance threatens to turn back the clock. Zyvox (linezolid) was the first in a new class of antibacterial drugs to treat serious infections resistant to other antibiotics has been approved by the Food and Drug Administration. Today, over 100 different antibiotics are available to cure minor to life threatening infections. Although antibiotics are useful in wide variety of infections, it is important to realize that antibiotics only treat bacterial infections.

Phthalides are a diverse group of metabolites produced by wide range of organisms from plants to fungi. Phthalides have many different biological activities. They can function as antibacterials, muscle relaxants, antivirals, effect cardiac functions and more [1]. Medically most prominent member of the family is mycophenolic acid, isolated from *Penicillium brevicompactum* as it's derivative mycophenolate mofetil is used as an immonosuppresant drug [2]. Phthalide is the base structure of the family, being the simpelest aromatic lactne. It's alkyl derivatives are naturally found in celery. Most of the aroma and taste of celery is due to butylphthalide and sedanolide. Phthalide natural products show a range of bioactivity, from enhancing flavors to slowing memory loss. Although diverse in function, these phytochemicals share a common structure: a benzene ring fused to a γ-lactone. Significant effort has been focused on synthesizing phthalides, but most asymmetric methods require chiral auxiliaries or chiral organometallics, few are catalytic, and none is atom-economical. herein we report an efficient and complementary route to synthesis several bioactive novel phthalides .

Materials and Methods

All the chemicals were purchased from Sigma-Aldrich and were used as supplied. Thin-layer chromatography (TLC) was performed on 0.25 mm pre coated silica gel 60 F254 aluminum sheets and column chromatography on silica gel 60 (0.063-0.2 mm) as well as silica gel 60 (<0.063 mm), products of Merck & Co. (Darmstadt, Germany). The C^{13} & H^{1}NMR spectra were recorded, with a Bruker (500 MHz) spectrometer, with TMS as internal standard.$CDCl_3$ was used as the solvent.

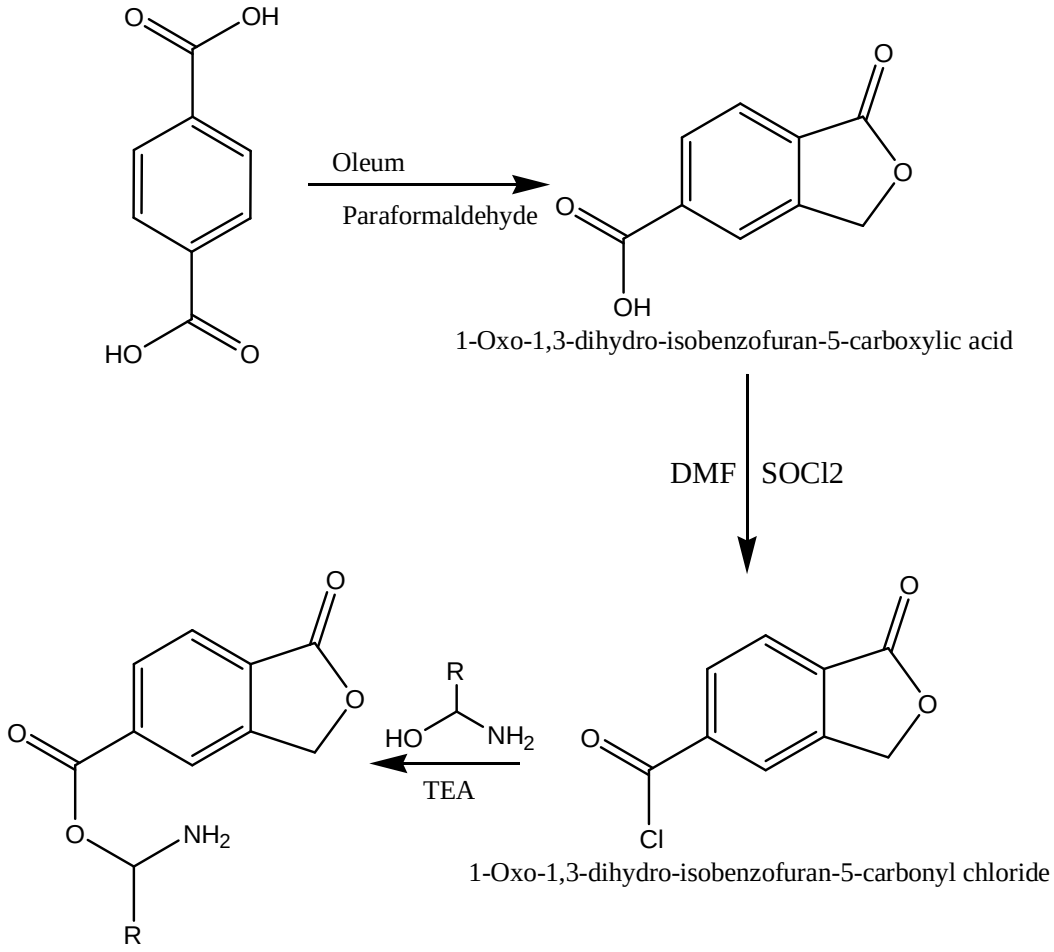
In-vitro antibacterial activity

The antimicrobial activity (bacteria) of the compounds was evaluated by agar well diffusion method (Ahmad and Beg, 2001)**.** All the microbial cultures were adjusted to 0.5 McFarland standards, which is visually comparable to a microbial suspension of approximately 1.5×10^8 cfu/ml (Andrews, 2001). 20ml of Muller Hinton agar media was poured into each petriplate and plates were swabbed with 100 µl inocula of the test microorganisms and kept for 15 min for adsorption. Using sterile cork borer of 8mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µl volume with concentration of 10 mg / ml compounds reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37°C for 24 hrs for Prediffusion. Antimicrobial activities of samples were evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi Antibiotic zone scale). The medium with DMSO as solvent was used as a negative control whereas media with ampicillin **(10mg/ml)** was used as positive control. The experiments were performed in duplicates.

Experimental

The overall reaction scheme is given below.

Scheme



R = H, CH3, C6H5, CH2CH3

Synthesis of 1-oxo-1,3-dihydro-isobenzofuran-5-carboxylic acid

Oleum (315ml) is charged into the round bottom flask. Terephthalic acid (100 gms) and then Paraformaldehyde (24 gms) is added. The mixture is then stirred at 110^0C to 160^0C for 8-12 hours. Quench the reaction mixture in ice and water and then temperature is adjusted to about 1000 C. The precipitate is filtered off, washed with water and suspended in water. The pH of the suspension is adjusted to about 7 with caustic lye. Then adjust the temperature of the reaction mass to about 70^0C-100^0C and filter it. The pH is adjusted to about 2 with concentrated HCl. The 5-carboxyphthalide precipitated is separated by filtration, washed and dried. Percentage of Purity: 98%

Synthesis of 1-oxo-1,3-dihydro-isobenzofuran-5-carbonyl chloride

5-carboxyphthalide (100gms) is suspended in toluene (500 ml) and thionylchloride (75 ml). N, N-dimethylformamide (4ml) is added and the mixture is heated at the reflux temperature for about 3 to 5 hours. Distilled the solvents in reduced pressure, to get the product in pure.

O-acylation using amino alcohols

The chloro derivative was taken in a double neck RB with a reflux condenser. Maintained the temperature below 10 oC.100 ml of chloroform was added to the reaction mixture. Slowly added the amino alcohol which was already weighed. 15 mL of triethyl amine was added using a dropping funnel. Stirred the reaction mixture for 4 hours. Washed with water, and filtered the precipitate and characterised.

Characterisation

Compound 1a: H^1NMR (500MHz,$CDCl_3$) δ (ppm):7.98, 6.54, 6.34, 6.33 4.37 ,3.59 . C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):173.7,165.7, 151.3,132.6, 129.9, 60.8, 44.3 22.7

Compound 2a: H^1NMR (500MHz,$CDCl_3$) δ (ppm):: H^1NMR (500MHz,$CDCl_3$) δ (ppm):7.58, 6.33, 6.34, 6.33 4.37 ,3.59 . C^{13}NMR (500MHz,$CDCl_3$) δ (ppm):177.7,168.1, 151.3,132.6, 129.9, 60.8, 44.3 22.7

Compound 3a: H^1NMR (500MHz,$CDCl_3$) δ (ppm):: H^1NMR (500MHz,$CDCl_3$) δ (ppm):7.93, 6.74, 6.52, 6.41 4.37 ,3.59 . C^{13}NMR (500MHz,$CDCl_3$) δ (ppm):173.7,165.7, 151.3,132.6, 129.9, 60.8, 44.3 22.7

Compound 4a: H^1NMR (500MHz,$CDCl_3$) δ (ppm):: H^1NMR (500MHz,$CDCl_3$) δ (ppm):7.66, 6.94, 6.34, 6.53 4.37 ,3.59 . C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):173.7, 169.7, 155.3,132.6, 129.9, 60.8, 44.3 22.7.

Results and Discussion

The phthalide derivatives were obtained by refluxing chloro carbonyl phthalide and amino alcohols in the ratio 1:1 was refluxed in chloroform medium with stoichiometric amount of triethyl amine (TEA) . Various derivatives has been made using different amino alcohols and evaluated the bacterial activity. The *in vitro* antibacterial activity of the synthesized compounds in DMSO against medically important Gram positive and Gram negative bacteria is shown in Table

Sample Name	Inhibition zone (mm/100µl)		
	E. coli	P. aureus	K. pneumonia
Control (ampicillin)	22	20	23
phathalide	16	18	19
1a	23	19	21
2a	16	17	15
3a	20	18	22
4a	25	19	25

The synthesised compounds shows better activity when compared to the control.

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