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Microwave Assisted Synthesis of Biologically Active Schiff's Bases

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Abstract

Bioactive aldehydes, 3-bromo-5-teritary butyl-2-hydroxy benzaldehyde, 5-di teritarybutyl-2-hydroxy benzaldehyde were synthesized, and characterized. Novel Schiff bases (S)-Methyl-2-N(3-bromo-5-tertiary butyl-2-hydroxy phenyl methelene) imino-3-methyl-oate derivatives were synthesized by the condensation of valine esters with 3-bromo-5-tertiary butyl-2-hydroxy benzaldehyde and 5-di teritarybutyl-2-hydroxy benzaldehyde under microwave conditions and characterized through IR, C^{13}, ^{1}H NMR and Mass spectral data. The Azomethine compounds were reduced to corresponding amines. All the synthesized compounds have been screened for antimicrobial activity and compared.

Keywords: (S)-Methyl-2-N(3-bromo-5-tertiary butyl-2-hydroxy phenyl methelene) imino-3-methylbutanoate, conventional method, microwave-irradiation, schiff base, spectral data, antimicrobial analysis

Introduction

The chemistry of the carbon-nitrogen double bond plays a vital role in the progresses of chemistry science. Schiff-base compounds have been used as fine chemicals and medical substrates. Recently multi-dentate complexes of iron and nickel showed high activities of ethylene oligomerization and polymerization. In our efforts for ligands of polymerization catalysts, synthesis of Schiff-base through classical condensation of aldehydes (or ketones) and amines were pursued, however, the yield of products were low. Cursory surveys of moieties/groups in organic molecules that generally possess anti-infective properties indicate the-CH = N-linkage pharmacophores. Schiff bases constitute a class of compounds that possess this group. Therefore the study was directed towards Schiff bases, their preparation, characterization and their biological

evaluation. Synthesis of Schiff base is often carried out with acid/base-catalyzed and generally by refluxing the mixture of aldehyde (or ketone) and amine in organic medium. However, with the assistance of microwave irradiation, it was found that the condensation reaction of substituted salicylaldehyde and various amines could proceed fast and efficiently without solvent

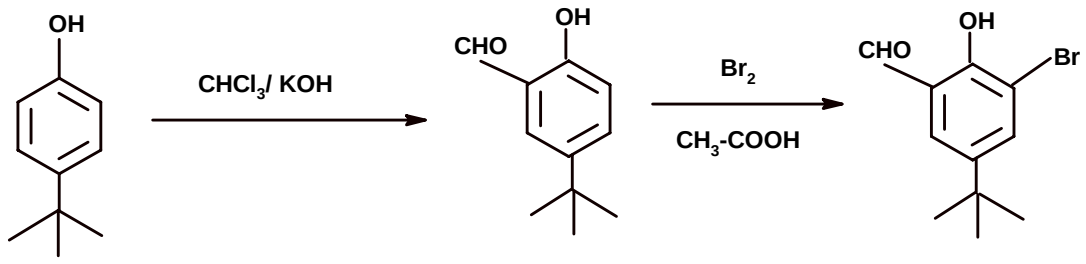
Materials and Methods

All bp's and mp's were uncorrected. The IR spectra were scanned with a Bruker spectrophotometer and only the pertinent values were expressed, in cm-^{1}. 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. The chemicalshift (d) and coupling constant (J) values were expressed in ppm and Hz only. The GLC analyses were carried out on a Shimadzu GC-7A chromatograph fitted with a flame ionization detector and glass packed column for routine analysis and a capillary column for the determination of isomeric compositions. The mass spectra (EI) was recorded at 70 eV with a Shimadzu GC-MS QP-1000A spectrometer. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

Synthesis of aldehydes

Synthesis of 3-bromo-5-teritarybutyl-2-hydroxy benzaldehyde-1

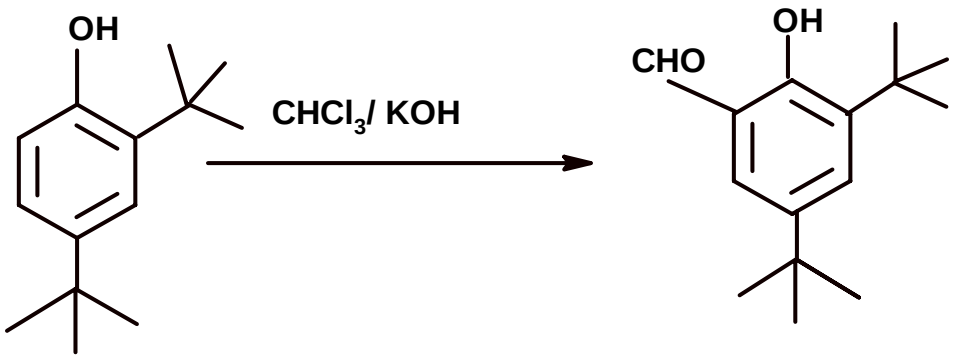
This compound synthesized starting with 5-teritory butyl phenol, by Reimerteiman reaction. 3, 5-diteritory butyl phenol was taken in a round bottom flask, 50 ml of chloroform was added slowly. Alcoholic potassium hydroxide was added slowly to the reaction flask. The progress of reaction was checked by TLC. After the completion, the reaction was quenched with water. The organic layer extracted with chloroform, and combined. The product obtained purified and brominated using liquid bromine and acetic acid.



Synthesis of 3, 5-di teritarybutyl-2-hydroxy benzaldehyde-2

This compound synthesized starting with 3, 5-diteritory butyl phenol, by Reimerteiman reaction. 3, 5-diteritory butyl phenol was taken in a round bottom flask, 50 ml of chloroform was added slowly. Alcoholic potassium hydroxide was added slowly to the reaction flask. The progress of reaction was checked by TLC. After the

completion, the reaction was quenched with water. The organic layer extracted with chloroform, and combined.

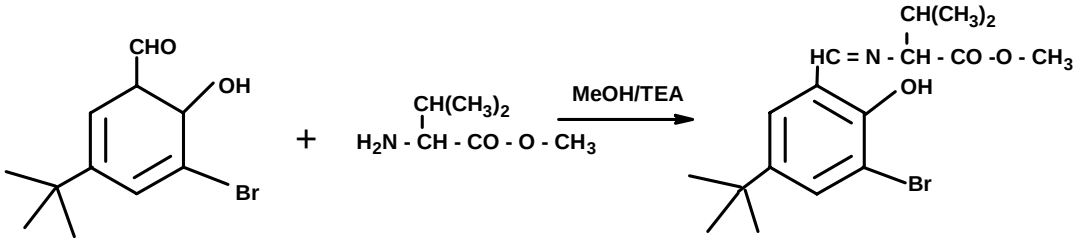


Synthesis of Schiff's bases

The microwave-assisted condensation of substituted benzaldehyde and amino acid ester were carried out in a domestic oven, Midea PJ21B-A 800W. 3 mmol 3-bromo-5-tertiary butyl-2-hydroxy benzaldehyde with equal mole Valine methyl ester were mixed together at ambient temperature in an Erlenmeyer flask (25 mL). The mixture was subjected to microwave for an optimized time on the "M-High" setting. The crude products were re-crystallized with ethanol.

Shiff's base-1

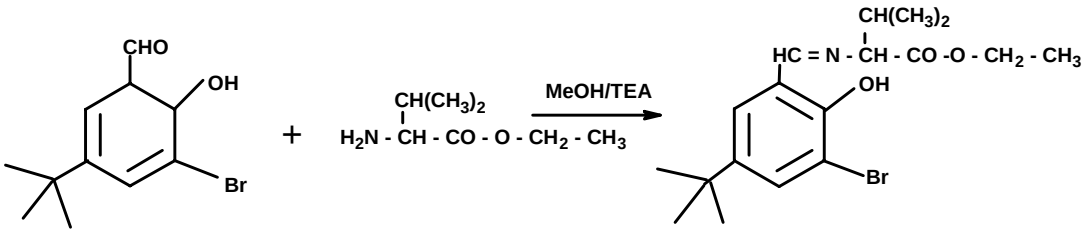
3-bromo - 5- tertiary butyl - 2-hydroxy benzaldehyde + Valine methyl ester - Schiff Base



The microwave-assisted condensation of substituted benzaldehyde and amino acid ester were carried out in a domestic oven, Midea PJ21B-A 800W. 3 mmol 3, 5-ditertiary butyl-2-hydroxy benzaldehyde with equal mole Valine methyl ester were mixed together at ambient temperature in an Erlenmeyer flask (25 mL). The mixture was subjected to microwave for an optimized time on the "M-High" setting. The crude products were re-crystallized with ethanol.

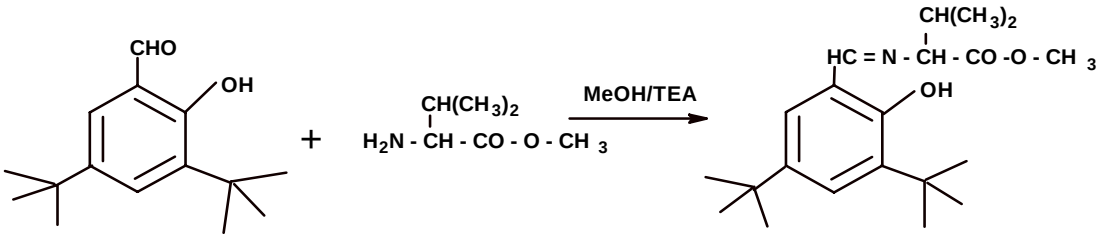
Schiff's base-2

3-bromo - 5- tertiary butyl - 2-hydroxy benzaldehyde + Valine ethyl ester - Schiff Base



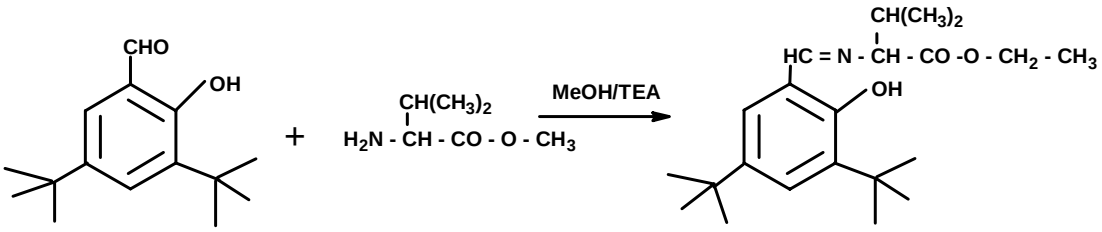
Schiff's base-3

3,5-ditertiary butyl-2-hydroxy benzaldehyde + Valine methyl ester



The microwave-assisted condensation of substituted benzaldehyde and amino acid ester were carried out in a domestic oven, Midea PJ21B-A 800W. 3 mmol 3, 5-ditertiary butyl-2-hydroxy benzaldehyde with equal mole Valine ethyl ester were mixed together at ambient temperature in an Erlenmeyer flask (25 mL). The mixture was subjected to microwave for an optimized time on the "M-High" setting. The crude products were re-crystallized with ethanol.

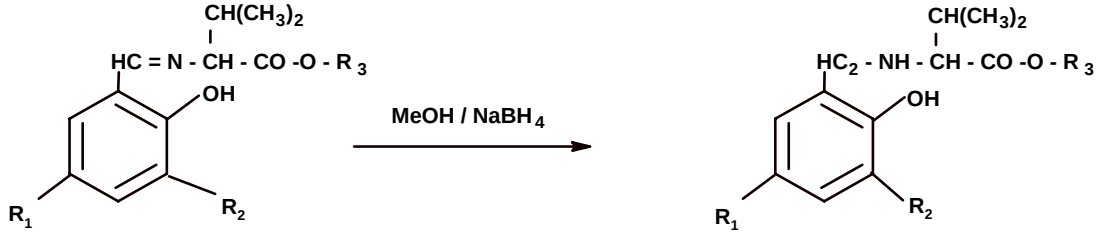
Schiff's base-4



Reduction of Schiffs bases

In a typical procedure, weighed quantities of synthesized Azomethine and sodium borohydride (Sigma Aldrich standard, Buchs, Germany) in the ratio of 1:1 was

allowed to react under stirring in methanol medium, at room temperature. The reaction was monitored by TLC (60/120 mesh, (Sigma Aldrich, Germany). After 2-3 h, the reaction was quenched with dil.HCl. Methanol was distilled off in a rotary evaporator and the residue was subjected to column chromatography.



R_1= tertiary butyl R_2= Br or tertiary butyl R_3= -O-CH_3 or -O-C_2H_5

Compound schiffs 1: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 5.17, 3.32, 2.54, 2.15-2.04, 1.29-1.650.88-0.91C^{13}NMR (500MHz, $CDCl_3$) δ ppm):171.2, 166.2, 155.7, 142.6, 133.4, 127.6, 118.5, 110.6, 60.3, 52.1, 34.0, 31.8, 31.3, 31.2, 21.0, 19.4, 18.0, 14.1. MS (EI) M+ = 370.28

Compound schiffs 2: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.23, 3.71, 2.34, 2.25-2., 1.38-1.62, 0.91-0.97. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):171.9, 159.5, 148.7, 133.63, 131.03., 130.8, 130.2, 124.3, 52.0, 34.0, 31.8, 31.3, 19.3, 19.1.1, 18.5, 17.2. MS (EI) M+ = 384.31

Compound schiffs 3: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.21, 3.18, 2.74, 2.12-2.04, 1.27-1.55, 0.81-0.93. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):171.6, 158.1, 140.1, 136.8, 127.4, 126.3, 117.6, 60.2 8, 51.9, 35.0, 34.1, 31.8, 29.4, 20.9, 19.4, 18.3, 14.1. MS (EI) M+ = 346.48

Compound schiffs 4: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.36, 3.53, 2.34, 2.15-2.24, 1.41-1.75-0.88-0.97. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):171.1, 158.2, 140.0, 136.8, 127.3, 126.2, 117.7, 60.9, 3, 34.1, , 31.7, 31.4, 29.4, 19.4, 18.3, 14.2, 14.1. MS (EI) M+ = 360.51

Compound reduced1: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.17, 3.63, 2.34, 2.11-2.23, 1.29-1.72, 0.86-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):170.7, 165.4, 152.6, 143.2, 131.4, 124.8 117.4, 60.3, 51.3, 35.4, 32.2, 31.4, 31.1, 24.3, 21.5, 17.4, 14.7 MS (EI) M+ = 372.3

Compound reduced 2: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.39, 3.19, 2.32, 2.12-2.21, 1.17-1.52, 0.71-0.89. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):170.5, 151.9, 131.6, 126.9, 124.3, 119.3, 58.8, 41.3, 31.4, 31.2, 29.7, 29.3, 25.6, 25.1, 23.0, 15.8. MS (EI) M+ = 386.5

Compound reduced 3: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.37, 3.59, 2.44, 2.11-2.17, 1.39-1.71, 0.89-0.93. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):170.3, 157.3, 142.6, 131.9, 129.2, 124.3, 118.5, 61.8, 42.3, 31.4, 31.2, 32.1, 27.8, 27.6, 25.6, 22.7, 14.7. MS (EI) M+ = 348.6

Compound reduced4: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 4.21, 3.29, 2.34, 2.08-2.14, 1.29-1.63, 0.89-0.95. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):170.1, 165.3, 139.6, 126.2, 121.3, 120.9, 118.2, 59.8, 40.3, 31.4, 31.2, 29.1, 29.0, 2.6, 25.6, 21.7, 16.5. MS (EI) M+ = 362.7

Compound aldehyde1: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 9.13, 7.4, 6.43, 6.11, 4.37, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):192.3, 165.7, 151.3, 132.6, 129.9, 44.3, 32.4, 32.0, 30.1, 29.8, 29.6, 27.6, 27.3, 23.1, 23.0, 22.7, 17.5. MS (EI) M+ = 257.4

Compound aldehyde2: H^1NMR (500MHz, $CDCl_3$) δ (ppm): 9.33, 7.4, 6.48, 6.11, 4.37, 1.29-1.65, 0.88-0.91. C^{13}NMR (500MHz, $CDCl_3$) δ (ppm):192.3, 165.7, 151.3, 132.6, 129.9, 44.3, 32.4, 32.0, MS (EI) M+ = 234.33

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 Aloin based compounds reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37°C for 24 hrs for Prediffusion. 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.

Results and Discussion

Bioactive aldehydes, 3-bromo-5-teritary butyl-2-hydroxy benzaldehyde, 5-di teritarybutyl-2-hydroxy benzaldehyde were synthesized, and characterized. The schiffs base obtained by refluxing synthesized aldehydes and amino acid methyl ester hydrochloride in the ratio 1:1 was refluxed in methanol medium with stoichiometric amount of triethyl amine (TEA). Micro wave mediated synthesis provided a rapid and high yield technique. Various Schiffs base derivatives has been made using different amino acid methyl ester. The imine esters further reduced to corresponding amine ester 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

Table 1: The *in vitro* antibacterial activity of the synthesized aldehydes and modified compounds (10 mg/ml)

Sample Name	Inhibition zone (mm/100µl)		
	E.coli	*P.aureus*	*K.pneumonia*
Control (ampicillin)	28	25	24
Ald-1	26	28	23
Ald-2	27	14	19
Schiff-1	19	23	15
Schiff-2	20	22	22
Schiff-3	28	29	25
Schiff-4	30	23	30
Reduc-1	31	19	29
Reduc-2	31	22	27
Reduc-3	19	19	11
Reduc-4	20	19	21

It is clear from the table that, the synthesized aldehydes exhibited comparable activity with the controle. Ie, Ampiciline. All the synthesized Schiffs bases exhibited very good activity towards the bacteria. The enhanced activity shows promise for application in various antimicrobial treatments.

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