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Suzuki Reaction for the Synthesis of New Derivatives of 4-Chloro-3,5-Dimethyl Phenol and their *in vitro* Antibacterial Screening

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Many derivatives of 4-chloro-3,5-dimethylphenol have been synthesized using Suzuki reaction and characterized by IR, ^{1}H NMR and micro elemental analysis. These compounds also tested in terms of their antibacterial properties against *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis*.

Keywords: 4-Chloro-3,5-dimethylphenol, Suzuki reaction, Antibacterial activity.

INTRODUCTION

Although extensive research has been conducted in the area of drug discovery, the demand for new types of antimicrobial agents continues to increase because of bacterial resistance to medical treatments, including sterilization and antibacterial treatment. Transition elements have been used as catalysts in the formation of new carbon-carbon bonds and have assumed great importance in this area, thereby providing new concepts for remarkable developments in organic synthesis [1-15]. Suzuki's interaction is widely used to prepare new compounds with unique properties and has enormous applications in various chemistry fields; for example, non-linear optics focuses on the behaviour of light in non-linear media [16]. Synthetic amino acids have played importance roles in biochemistry as building blocks in designing peptide-based biologically active molecules [17], anti-HIV molecules [18], anti-HCV molecules [19], treatments of infections caused by Gram-positive bacteria (vancomycin) [20], carbon nanotubes [21], *etc*. In this work, and in continuation of our works to synthesize and evaluate some derivatives of pyrimidine toward HIV, cyclin-dependent kinase 2 (CDK2) inhibitory activities, many important types of fungi [22,23], performed organic aggregation using Suzuki's reaction to disinfectant 4-chloro-3,5-dimethylphenol for the purpose of increasing its effectiveness to treat resistant pathogenic bacteria. *Staphylococcus aureus* is part of conventional microbiota present in the upper respiratory tract [24], skin and in the gut mucosa [25]. *Escherichia coli* belongs to a group of bacteria colloquially known as coliforms found in the gastrointestinal tract of warm-blooded animals [26] and it is also the primary facultative anaerobe of human gastrointestinal tract [27]. *Proteus mirabilis* can increase the level of urease after a series of transformations, thereby forming kidney stones and eventually causing kidney failure; this microorganism can also cause wound infections, pneumonia and septicemia in hospitalized patients [28].

EXPERIMENTAL

Melting points are uncorrected and were measured with a strut melting point apparatus (England). FT-IR were measured by TENSOR II FTIR spectrometer from Brucker company using KBr pellets. ^{1}H NMR data were obtained on 400 MHz (1H) spectrometer (Bruker, Tehran Medical University) using DMSO-d_6 solvent with tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed on a PE-2400 elemental analyzer. All the solvents and reagents were obtained commercially from Aldrich, Fluka. Silica gel (0.040-0.063 mm) used for analytical silica gel TLC plates 60 F_{254} were purchased from Merck and the compounds were detected by their absorption under UV light.

General synthesis of 4-chloro-3,5-dimethyl phenol derivatives using Suzuki method (7-12): In 25 mL round bottom

flask equipped with reflux condenser, 0.0004 mol of 4-chloro-3,5-dimethyl phenol mixed with appropriate quantity of aryl boronic acid (**1-6**) and 0.05 g of $Pd(PPh_3)_4$ were added into the flask containing 20 mL of absolute ethanol under inert atmospheric condition (N_2) gas. The mixture was stirred and heated and 5 mL of solution (5 % Na_2CO_3) were added into the flask. The reaction mixture was stirred and heated at 75 ºC for 5-6 h then followed by TLC and monitor reactions using (*n*-hexane and ethyl acetate) in 2:3 ratio v/v. The mixture was filtrated off to remove the inorganic salt and the residue of pallidum catalyst, washed by cooled ethanol and the solvent was removed and decanted by cooled ether (**Scheme-I**).

4′-Hydroxy-2′,6′-dimethyl-[1,1′-biphenyl]-3-carbaldehyde (7): Prepared from 4-chloro-3,5-dimethyl phenol (0.20 g, 0.001 mol) and 3-(formylphenyl)boronic acid (0.28 g, 0.001mol) solid white; yield 85 %; R_f = 0.88; m.p. 217-220 ºC. FT-IR (KBr, cm^{-1}): 3393, 2750, 1692, 1596-1551. ^{1}H NMR (DMSO-d_6): ? 2.26(t, 6H), 6.48-6.90 (m, 4H), 7.02-7.85 (m, 4H), 9.07 (s, 1H), 10.43 (bs, 1H). Anal. for $C_{15}H_{14}O_2$ calcd. (found) %: C, 79.62 (79.51); H, 6.24 (6.10).

4′-(Diphenylamino)-2,6-dimethyl-[1,1′-biphenyl]-4-ol (8): Prepared from 4-chloro-3,5-dimethylphenol (0.20 g, 0.001 mol) and (4-(diphenylamino)phenyl)boronic acid (0.46 g, 0.001 mol). Solid white; yield 92 %; R_f = 0.85; m.p 213-217 ºC; FT-IR (KBr, cm^{-1}): 3394, 3061, 1589-1548. ^{1}H NMR (DMSO-d_6): δ 2.38 (t, 6H), 6.48-6.94 (m, 4H), 7.02-7.86 (m, 14H), 10.35-10.38 (bm, 1H). Anal. $C_{26}H_{23}NO$ calcd. (found) %: C, 85.45 (85.31); H, 6.34 (6.22); N, 4.38 (4.29).

2,6-Dimethyl-2′-(ferrocene)-[1,1′-biphenyl]-4-ol (9): Prepared from 4-chloro-3,5-dimethyl phenol (0.20 g, 0.001 mol) and ferrocene boronic acid (0.38 g, 0.001 mol). Yield: 89 %, solid orange; R_f = 0.80; m.p. 244-246 ºC; FT-IR (KBr, cm^{-1}): 3499, 1557-1407. ^{1}H NMR (DMSO-d_6): δ 2.20 (t, 6H), 6.49-6.99 (m, 4H), 7.23-7.88 (m, 8H), 10.47 (bs, 1H). Anal. for $C_{18}H_{16}OFe$ calcd. (found) %: C, 71.08 (71.01); H, 5.30 (5.16).

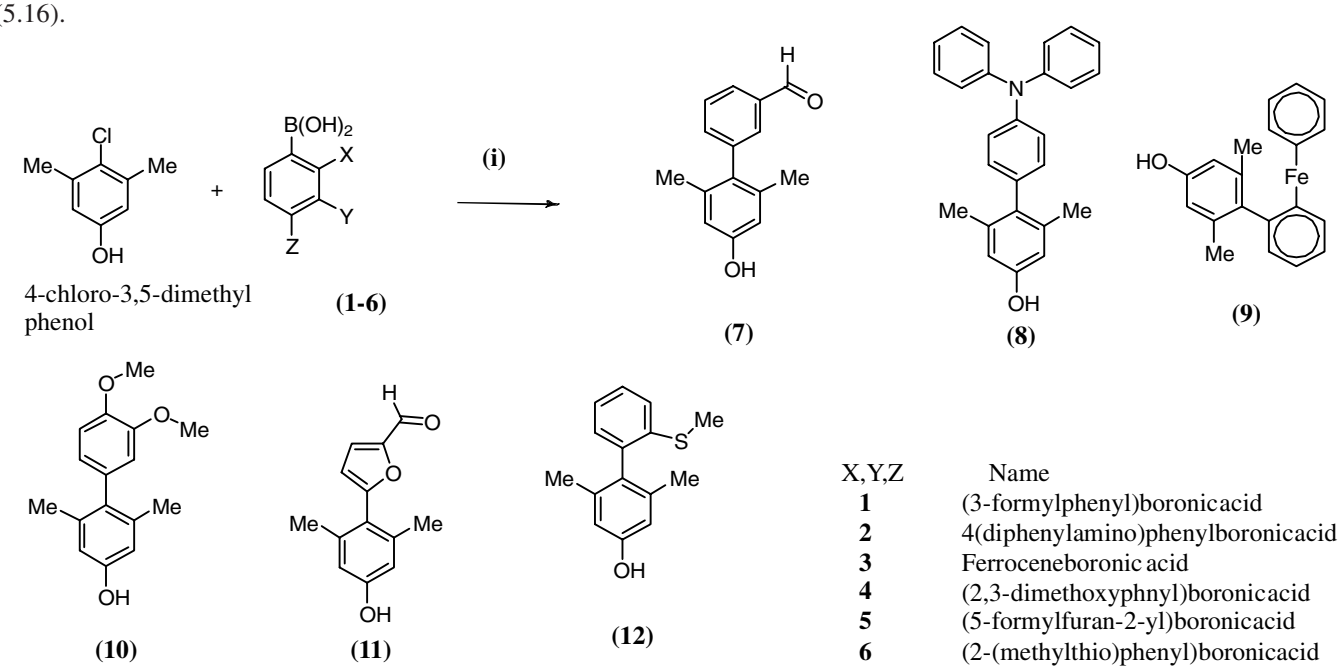
3′,4′-Dimethoxy-2,6-dimethyl-[1,1′-biphenyl]-4-ol (10): Prepared from 4-chloro-3,5-dimethyl phenol (0.20 g, 0.001 mol) and (3,4-dimethoxyphenyl)boronic acid (0.33 g, 0.001 mol). Solid white, yield 95 %; R_f = 0.80; m.p.: 217-218 ºC; FT-IR (KBr, cm^{-1}): 3390, 1584-1553. ^{1}H NMR (DMSO-d_6): δ 1.10 (m, 2H), 2.17 (m, 2H), 3.42 (m, 6H), 7.07-7.93 (m, 3H), 10.43 (bs, 1H) Anal. for $C_{16}H_{18}O_3$ calcd. (found) %: C, 74.40 (74.36); H, 7.02 (6.79).

5-(4-Hydroxy-2,6-dimethylphenyl)furan-2-carbaldehyde (11): Prepared from 4-chloro-3,5-dimethyl phenol (0.20 g, 0.001 mol) and (5-formylfuran-2-yl)boronic acid (0.27 g, 0.001 mol). Solid orange yellow; yield 90 %; R_f = 0.80; m.p.: 217-220 ºC; FT-IR (KBr, cm^{-1}): 3393, 2750, 1692, 1596-1551. ^{1}H-NMR (DMSO-d_6): δ 2.32 (t, 6H), 6.66-7.08 (m, 4H), 7.20 (d, 1H, *J* = 8), 7.51 (d, 1H, *J* = 7.9), 9.84 (bs, 1H), 10.09 (m, 1H). Anal. for $C_{13}H_{12}O_3$: C, 72.21 (72.11); H, 5.59 (5.49).

2,6-Dimethyl-2′-(methylthio)-[1,1′-biphenyl]-4-ol (12): Prepared from 4-chloro-3,5-dimethyl phenol (0.20 g, 0.001 mol) and (2-(methylthio)phenyl)boronic acid (0.31 g, 0.001 mol) solid umber; Yield 89%; R_f = 0.81; m.p.: 279-280 ºC; FT-IR (KBr, cm^{-1}): 3347, 2989, 2917, 1574, 1427, 1001, 946. ^{1}H NMR (DMSO-d_6): δ 1.15, (s, 3H), 2.17 (t, 6H), 6.55-6.86 (m, 4H), 7.07-7.93 (m, 4H), 10.36 (bs, 1H). Anal. for $C_{15}H_{16}O_S$: C, 73.73 (73.69); H, 6.60 (6.49).

Biological activity: *S. aureus*, *E. coli* and *P. mirabilis* were obtained from Department of Biology, College of Science, University of Babylon, Babylon, Iraq. The culture was prepared by dissolving 40 g of potato dextrose agar powder in the minimum amount of distilled water and then made up the volume upto 1000 mL. The solution was then sterilized in autoclave at 121 ºC and 15 lb/in^2 steam pressure for 20 min. This medium was used for determination of optimum culture media for inhibition process.

Antibacterial bioassays were performed on petri dish plates contains 20 mL of standard potato dextrose agar powder.



4-chloro-3,5-dimethyl phenol

(1-6)

(7)

(8)

(9)

(10)

(11)

(12)

X,Y,Z	Name
1	(3-formylphenyl)boronic acid
2	4(diphenylamino)phenylboronic acid
3	Ferroceneboronic acid
4	(2,3-dimethoxyphnyl)boronic acid
5	(5-formylfuran-2-yl)boronic acid
6	(2-(methylthio)phenyl)boronic acid

(i) Na_2CO_3 5% , $Pd(PPh_3)_4$, closed system(N_2) gas, Absolute ethanol irradiated (15-20) min

Scheme-I

TABLE-1
INHIBITION ZONE FOR 4-CHLORO-3,5-DIMETHYL PHENOL DERIVATIVES (**7-12**)

Compounds	Concentration (μg/mL) in DMF	Zone of inhibition in mm* (Antibacterial activity)		
		S. aureus	*E. coli*	*P. mirabilis*
7	1000	13 ± 0.25	14 ± 0.30	14 ± 0.25
8	1000	10 ± 0.25	11 ± 0.25	09 ± 0.25
9	1000	13 ± 0.25	16 ± 0.25	12 ± 0.20
10	1000	15 ± 0.35	15 ± 0.25	14 ± 0.25
11	1000	22 ± 0.25	18 ± 0.25	16 ± 0.25
12	1000	22 ± 0.25	18 ± 0.30	16 ± 0.25
Gentamycin	1000	22 ± 0.25	20 ± 0.30	21 ± 0.25
Control (DMF)	–	–	–	–

*Diameter of well (bore size) – 5 mm

After the mycelia colonies were developed, 3 wells of 0.5 cm in diameter were made 1 cm from the rim. Antibiotic (1 mL) was added to the wells and the plates were incubated at 25 ºC for 5 days. The stability of antibacterial compounds was monitored by using FT-IR spectrum for each compound (one measure every 1 week). The spectrum was obtained for compounds that stored in refrigerator (2-8 ºC). There was no change in the FT-IR spectrum interpreted as a change in the structure of the corresponding compound.

RESULTS AND DISCUSSION

4-Chloro-3,5-dimethylphenol was selected as precursor to react with various substituted aryl boronic acid (**1-6**) in the presence of pallidum *tertakis*-triphenyl phosphine [$Pd(PPh_3)_4$] as catalyst and 5 % of Na_2CO_3 solution in ethanol . Upon reflux for 5-6 h, the compounds (**7-12**) having yield 85-92 % were generated. Nitrogen gas was used as an inert gas in a closed system in ordet to prevent the oxidation of catalyst used and its conversion into palladium oxides [29-31] and Na_2CO_3 as base was used to get a high yield of the reaction. Similarly, cordinated palladium complex accelerated the transmetallation step due to the formation of (Ar-PdL_2-OH) from (Ar-PdL_2-X) (Suzuki reaction) [29]. All the prepared organic compounds were identified through infrared, ^{1}H NMR spectra and microelement analysis.

The structure of compound **7** was confirmed by IR spectrum showing the absorption vibration bands at 3393 cm^{-1} ν(OH), 2750 cm^{-1} ν(CH aldehyde), 1692 cm^{-1} ν(CH=O). The chemical shift of ^{1}H NMR was triplet at δ = 2.26 for two methylene groups, δ = 6.48 multiplet for two CH_2 in benzene ring, δ = 7.02-7.85 multiplet for the protons in benzene ring system, δ = 9.07 singlet for the proton in OH group and the appearance multiplet of δ = 10.43 ppm for proton in CHO group. This observation was consistent with the structure of compound. In the same manner, compounds **8** exhibited the characteristics vibration bands at 3394 cm^{-1} ν(OH), 3061, 1589, 1548 cm^{-1} ν(CH arom.). The chemical shift at δ = 2.38 ppm triplet was observed for two methyl groups, δ = 6.48-6.94 multiplet for two CH_2 groups, δ = 7.02-7.86 multiplet for all protons of π-π conjugated system in benzene ring and δ = 10.38 for proton in OH group.

The chemical structure of compound **9** was similar to other compounds, but a distortion was observed in the form of absorption band in the IR and ^{1}H NMR spectrum. In IR, the characteristics vibration bands at 3419 cm^{-1} ν(OH), 1557 and 1407 cm^{-1} ν(CH) for conjugated double bond in aromatic system for ^{1}H NMR δ = 2.20, 6.49-6.99, 7.23-7.88, 10.47 ppm are the characteristics chemical shifts of 2 CH_3, 2 CH_2, protons of aromatic rings and one proton of OH group, respectively. As such, the spectral diagnosis of compound **9** was confirmed. Compound **10** was formed by reaction of the parent compound (4-chloro-3,5-dimethylphenol) with (3,4-dimethoxyphenyl) boronic acid (**4**), which exhibited the IR vibration bands at 3390 ν(OH), 2835 ν(OMe) and 1584-1553 ν(CH arom.). ^{1}H NMR revealed the peaks at δ = 1.10, 2.17, 3.42-3.82, 6.55-6.86, 7.07-7.93 and 10.43 ppm for 2*p*-OMe, 2*m*-OMe, 2Me, 2×CH_2, CH aromatic and OH, respectively. Compound **11** differed in the appearance of carbonyl absorption band at 1696 cm^{-1} in IR spectrum and chemical shift δ = 10.07-10.09 ppm, which is due to aldehyde-compensated group on the heterocyclic ring (furan). Moreover, compound **12** had C-S absorption band vibrating at 757 cm^{-1} in IR spectrum and singlet for two methyl groups attached to a sulfur atom.

Antifungal activity: The results showed all compounds have fine activity against *S. aureus*, *E. coli* and *P. mirabilis* with different zone of inhibition. Also compounds **11** and **12** exhibited the most active compounds against above-mentioned bacteria (Table-1).

Conclusion

In this work, a new series of 4-chloro-3,5-dimethyl phenol derivatives (**7-12**) synthesized using Suzuki reaction and evaluated for antibacterial activity. In comparison with standard gentamycin, compounds **11** and **12** were found to be the most active analogue against the studied bacteria. Therefore, these compounds could be promising agent for further structural modification and pharmacological and toxicity evaluation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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