



Synthesis, characterization and biological activity of azides and its derivatives

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Received 20 June 2020; Accepted 5 October 2022

ABSTRACT

Being highly reactive and polar in nature, azide and their derivative are shown to be appreciably active for antibacterial activities. Azide synthesized compounds are the key tools of active research because of their reactivity and polar character. The target of the present work is to synthesize 4-hydroxyphenyl azide, 4-nitrophenyl azide and their derivative by adopting the synthetic route. The adoption of this technique is to achieve optimized yield by using different solvents and reactants and their structure determination is carried out by using UV-Vis, Fourier-transform infrared spectroscopy and gas chromatography–mass spectrometry techniques. The presented study depicts the multistep synthesis of 4-hydroxyphenyl azide (85%–93%), 4-nitrophenyl azide with unsaturated sodium azide (90%–92%), 3-bromo-4-hydroxyphenyl azide (85%–92%) and 2-bromo-4-nitrophenyl azide (96%) with N-bromosuccinimide. The synthesized compounds have shown remarkable antibacterial activities against all pathogens and K, S, L compounds have inhibited the bacterial growth in the range of (22, 13, 17, 9 mm), (24, 14, 14, 12 mm), (22, 7, 5, 5 mm) against bacterial species (*Bacillus subtilis*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Agrobacterium tumefaciens*) more effectively.

Keywords: Azides; Synthesis; Derivatives; Biological activity; Characterization

1. Introduction

The first organic phenyl azide was synthesized by Peter Grieb in 1864. After the discovery of organic azides, they were studied in every field of chemistry especially in organic chemistry [1,2]. Organic azides are of paramount importance in organic synthesis as can be used as precursors for the synthesis of nitrogen containing organic compounds such as amines, nitrene, nitrenium ions, aziridines, azirines and triazenes etc. [3,4]. In addition, organic azides can be easily transformed into amines, isocyanates etc. [5,6]. Azides are used as amino protecting group, and has

advantageous features over carbamates and amides such as less steric hindrance, greater solubility [7]. Organic and inorganic azides have explosive properties which are considered as first energy – rich molecules. The nitrogen gas and nitrene group is released due to exothermic dissociation. In general, the organic compounds having azido group causes the increase its energy content by approx. 290–355 kJ/mol [2,8,9]. Organic azides are known as versatile intermediates in the construction of cyclic nitrogen-containing compounds [10–13] and polymer cross linking agents [14]. In 1950s, organic azides achieved remarkable interest because of their applications in the chemistry of acyl, aryl, and alkyl

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azides [15,16]. Organic azides are interested in industrially, agriculturally and pharmaceutically such as in the synthesis of heterocyclic compounds (triazoles and tetrazoles) moreover used in blowing agents and the remarkable international heed of the azidonucleosides in the treatment of AIDS [17]. Metal azides are served as detonators in explosive technology. The use of sodium azide is in airbags [18,19].

In this article, we have synthesized p-hydroxy phenyl azides and p-nitrophenyl azides in chemistry lab of Lahore College for Women University by adopting cost and effective materials. We have compared the reaction time and yield of the synthesized compounds by using different acids and strong base/weak acid such as HCl, H₂SO₄, CH₃COOH and DMSO. From these synthesized compounds, we have synthesized novel compounds such as 3-bromo-4-hydroxyphenylazide and 2-bromo-4-nitrophenylazide by the substitution reactions. The structures of all synthesized compounds was elucidated using different physical, analytical tools and also antibacterial activity. Agar dilution method is used to determine the inhibition of all synthesized compounds and act as antibacterial agents [20].

2. Experimental

In this research work, 4-hydroxyphenyl azide was synthesized by using different solvents such as CH₃COOH(1H), HCl(1I), H₂SO₄(1J), DMSO(1K).

2.1. Solvent mediated synthesis of 4-hydroxyphenyl azide 1(H-K)

Compounds 1(H-K) were synthesized by using different reactants, taken in different quantities. This reaction was completed in two steps. In the first step, para-nitrophenol (0.3 g), Zn-dust (0.4 g), water (3 mL) and acids (2 mL) like CH₃COOH(1H), HCl(1I), H₂SO₄(1J), DMSO(1K) were taken in a round a bottom flask. Then these different mixtures were heated for 5, 6, 7 and 4 h at 240°C and the first step of this reaction was regularly checked by TLC (2 mL ethanol, 3 mL *n*-hexane). In the second step, the ice bath was prepared in which the above-synthesized mixture was cooled at 0°C. In the whole procedure, stirring is done in both steps continuously. Then first added NaNO₂ (0.03 g) and then NaN₃ (0.04 g). The pure product was achieved by washing it with diethyl ether (3 × 10 mL) and traces of aqueous solvent were removed. Thus, 1(H-K) oily compounds were synthesized. The synthetic route of compounds 1(H-K) is shown in Fig. 1.

2.2. Solvent mediated synthesis of 4-nitrophenyl azide 2 (S-T)

Compounds 2 (S-T) were synthesized by using different reactants in different quantities. In the first step, paste was made by using of 4-nitroaniline (1.3 g) with combination of two acids like HCl (10 mL) and HNO₃ (5 mL) for S compound and with H₂SO₄ (10 mL):CH₃COOH (5 mL) for T compound and then heated for 4 h at 18°C. When the 4-nitrophenol reactant was dissolved completely then added urea (0.8 g), NaNO₂ (1.7 g) and NaN₃ (1 g). After the addition of each reactant, stir it continuously for 1 h. An impure product was obtained, washed it with brine then

dried it and recrystallized with chloroform and petroleum ether. The synthetic route of compounds 2 (S-R) is shown in Fig. 2.

2.3. Synthesis of 3-bromo-4-hydroxyphenyl azide

3-bromo-4-hydroxyphenyl azide (1L) was synthesized by using different reactants, taken in different quantities. One step procedure proceeded in sealed tube contained DCM (3 mL), 4-nitrophenyl azide (0.03 mL), NBS (0.07 g) and FeCl₃ (0.1 g). The mixture was heated at 80°C for 12 h. The organic layer was separated by washing with diethyl ether (3 × 10 mL) and the solvent was removed by rotary evaporator and recrystallized with chloroform (5 mL) and ethyl acetate (7 mL). The synthetic route of this compound is shown in Fig. 3.

2.4. Synthesis of 2-bromo-4-nitrophenyl azide (2U)

Compound 2U was synthesized by using different reactants, taken in different quantities. One step procedure was completed in sealed tube contained DCM (3 mL), 4-nitrophenyl azide (0.03 mL), NBS (0.07 g) and FeCl₃ (0.1 g), the mixture was heated at 80°C for 12 h. The organic layer was separated by washing with diethyl ether (3 × 10 mL) and the solvent was removed by rotary evaporator and recrystallized with chloroform (5 mL) and ethyl acetate (7 mL). The synthetic route of this compound is shown in Fig. 4.

3. Results

This research work describes the detailed study and wide scope of azides and its derivatives. The compounds 4-nitrophenyl azide, 4-hydroxyphenyl azide, 2-bromo-4-nitrophenyl azide, 3-bromo-4-hydroxyphenylazide were synthesized due to their various applications and remarkable properties. Additionally, various stains were used for their antimicrobial screening. The progress of the reaction was checked by TLC after regular intervals and characterization were done through various techniques such as UV-Vis,

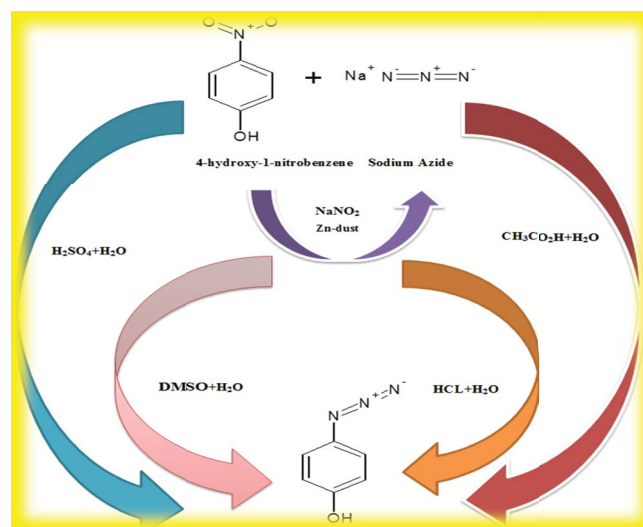


Fig. 1. Synthesis of 4-hydroxyphenyl azide 1 (H-K).

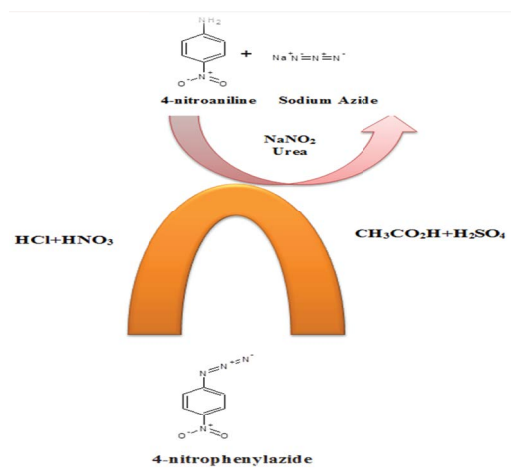


Fig. 2. Synthesis of 4-nitrophenyl azide 2 (S-T).

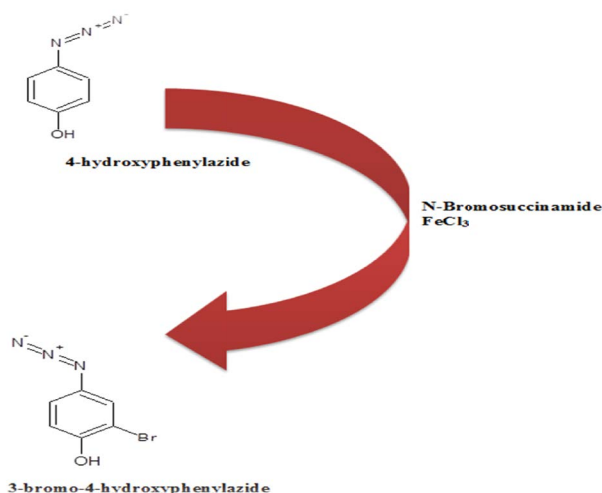


Fig. 3. Synthesis of 3-bromo-4-hydroxyphenyl azide (1L).

Fourier-transform infrared spectroscopy (FTIR), GC-MS. The melting, boiling point and solubility test provided valid information about the synthesized compounds.

3.1. Compounds 1(H-K)

Qian Cai in 2004 synthesized 4-azidophenol by using 4-iodophenol, sodium azide, CuI, etc. and the final product was achieved with an 84% yield by using solvent DMSO [21] that was compared with the yields of above-synthesized compounds. Comparison of conventional synthesis of compounds 1(H-K) through solvent-mediated Zn dust reduction method is shown in Table 1.

UV-Visible spectroscopic analysis was done on the "Hitachi U-2800" double beam spectrophotometer. Compounds 1(H-K) showed their absorption peaks in the range of 220–260 and 298–354 nm. First range was due to the attachment of azide group to the phenyl ring that is unsaturated and due to the $\pi-\pi^*$, $n-\pi^*$ transitions. The second range was due to the attachment of auxo groups to the phenyl

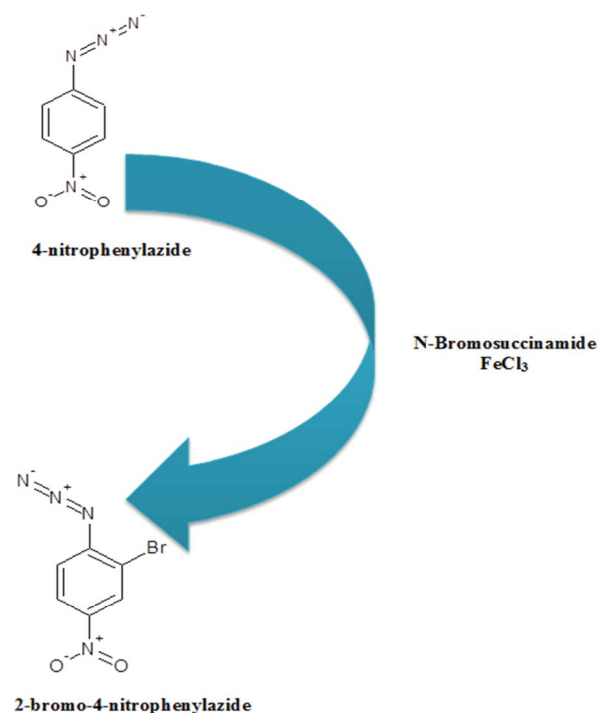


Fig. 4. Synthesis of 2-bromo-4-nitrophenyl azide (2U).

ring, OH group causes the redshift and its lone pair is conjugated with the phenyl ring.

FTIR analysis was done using the Midac FTIR spectrophotometer (M-2000) using KBr disc within the range of 500–4,000 cm^{-1} . Synthesized organic compounds showed various absorption bands that were 1,400–1,600 cm^{-1} indicated the aromaticity, 675–900 cm^{-1} , 1,000–1,300 cm^{-1} , 2,115.91 cm^{-1} , 2,347.37 cm^{-1} , 3,200–3,550 cm^{-1} , 1,180–1,390 cm^{-1} indicated that C–H in a plane and out of plane bending N=N=N-stretching, unsaturation adjacent to azide group, O–H and C–O stretching.

Mass Spectrum showed that the base peak appeared at 45 m/z and the molecular ion peak was at 139 m/z that is very near to its molecular weight. Other peaks such as 42, 105, 107 and 119 m/z showed the presence of azide and other fragments. The phenyl group was indicated by the peak at 77 m/z . Thus, all these peaks provided evidence for the synthesis of azides.

3.2. Compounds 4-nitrophenyl azide 2(S-T)

Di Qui in 2013 produced aryl azides from aryl amines and tributylstannyl azide in the presence of CH_3CN and TsOH to get a 75% yield [22] that was compared with the yields of above-synthesized compounds by using cheap materials. A comparison of conventional synthesis of compounds 4-nitrophenyl azide 2 (S-T) through solvent-mediated using urea is shown in Table 2.

UV-Visible spectroscopic analysis was done on the "Hitachi U-2800" double beam spectrophotometer. Synthesized organic compounds 2(S-T) showed absorption peaks in the range of 222–224 and 320–322. The first range

Table 1
Comparison of conventional synthesis of compounds 1(H-K) through solvent-mediated Zn dust reduction method

Method used (conventional)	Solvent-mediated			
	CH ₃ CO ₂ H:H ₂ O	HCl:H ₂ O	H ₂ SO ₄ :H ₂ O	DMSO:H ₂ O
Reactants	4-nitrophenol	4-nitrophenol	4-nitrophenol	4-nitrophenol
Reagents	Sodium nitrite	Sodium nitrite	Sodium nitrite	Sodium nitrite
	Sodium azide	Sodium azide	Sodium azide	Sodium azide
Solvent for extraction	Diethyl ether	Diethyl ether	Diethyl ether	Diethyl ether
Reaction time	6 h	5 h	7 h	4 h
Products	4-hydroxyphenyl azide	4-hydroxyphenyl azide	4-hydroxyphenyl azide	4-hydroxyphenyl azide
Yield	85%	90%	89%	93%
B.P.	78°C	80°C	84°C	79°C
UV-Vis (cold H ₂ O)				
λ_{\max} nm	246, 298 nm	220, 310 nm	224, 316 nm	260, 354 nm
FTIR (cm ⁻¹)	2,115.91; 2,347.37;	2,115.91; 2,347.37;	2,115.91; 2,347.37;	2,115.91; 2,347.37;
	334.92; 1,506.41;	334.92; 1,506.41;	3,323.35; 1,506.41;	334.92; 1,506.41;
	1,095.57 cm ⁻¹	1,112.93 cm ⁻¹	1,095.57 cm ⁻¹	1,112.93 cm ⁻¹
Gas chromatography–mass spectrometry		42, 45, 77, 93, 105, 109, 131, 139 m/z		42, 45, 77, 93, 105, 109, 131, 139 m/z

Table 2
Comparison of conventional synthesis of compounds 2(S-T) through solvent-mediated using urea

Method used (conventional)	Solvent-mediated	
	HCl:HNO ₃	H ₂ SO ₄ :CH ₃ COOH
Reactants	4-nitroaniline	4-nitroaniline
Reagents	Sodium nitrite	Sodium nitrite
	Sodium azide	Sodium azide
Recrystallization	Chloroform	Chloroform
	Petroleum ether	Petroleum ether
Solvent for washing compounds	Water and brine	Water and brine
Reaction time	5 h	6 h
Products	4-nitrophenyl azide	4-nitrophenyl azide
Yield	92%	90%
M.P.	98°C	60°C
UV-Vis (cold H ₂ O) λ_{\max} nm	222, 322 nm	224, 320 nm
FTIR (cm ⁻¹)	2,119.77; 2,258.64; 1,489.05;	2,119.77; 2,256.71; 1,489.05;
	812.03; 1,286.52; 3,101.54 cm ⁻¹	810.10; 1,286.56; 3,101.54 cm ⁻¹
Gas chromatography–mass spectrometry	42, 45, 91, 77, 119, 129, 131, 135, 16 m/z	42, 45, 91, 77, 119, 129, 131, 135, 167 m/z

was due to the existence of the unsaturated group, associated with a phenyl ring, that is azide and due to the $\pi-\pi^*$ and $n-\pi^*$ transitions. The second-range was due to an auxochromic group that is NO₂ having extended conjugation with phenyl ring which caused the redshift.

FTIR analysis was done using the Midac FTIR spectrophotometer (M-2000) using KBr disc within the range of 500–4,000 cm⁻¹. Synthesized organic compounds 2(S-T) were showed IR absorption bands in the range of 860.52 and 894.97 cm⁻¹, 2,119.77 cm⁻¹, 1,286.52 cm⁻¹, 1,400–1,600 cm⁻¹,

3,000–3,100 cm⁻¹, 675–900 cm⁻¹, 800–840 cm⁻¹ indicating that C–N stretch, N=N=N⁻ stretching, N–O stretch, aromaticity, >C=C stretching, C–H in plane and out of plane bending and p-substitution.

Mass Spectrum showed that base peak at 45 m/z. Its molecular ion peak came at 167 m/z that is very near to its molecular weight and other peaks such as 42, 131, 91 and 119 m/z showed the presence of azide and other fragments. Phenyl group was indicated by the peak at 77 m/z. Thus, all these peaks gave evidence for the synthesis of azides.

3.3. Compounds (1H, 2S)

Comparison of conventional synthesis of compounds (1H, 2S) through solvent-mediated using Zn-dust and urea is shown in Table 3.

3.4. Compounds (1L, 2U)

Jawad in 2012 synthesized arylzide from the phenacyl bromide derivative with 80% yield [23] and its yield was compared with the above-synthesized compounds. Comparison of compounds (1L, 2U) through solvent-mediated by using different reactants catalyzed FeCl₃ method is shown in Table 4.

UV-Vis data indicated that the synthesized organic compounds 1L and 2U showed absorption peaks in the range of 222–288 and 342–356. The first range was due to the existence of the unsaturated group, associated with a phenyl ring, that is azide and due to the π - π^* and n - π^* transitions. The second-range was due to an auxochromic group that is NO₂ and OH groups having extended conjugation with phenyl ring which caused the redshift.

FTIR analysis was done using the Midac FTIR spectrophotometer (M-2000) using KBr disc within the range of 500–4,000 cm⁻¹. Synthesized organic compounds 1L, 2U were showed IR absorption bands in the range of 2,115.91 cm⁻¹, 2,347.37 cm⁻¹, 1,400–1,600 cm⁻¹, 3,000–3,100 cm⁻¹, 1,296.61 cm⁻¹, 515–690 cm⁻¹ indicated that N=N=N⁻ stretching, saturated

Table 3

Comparison of conventional synthesis of compounds (1H, 2S) through solvent-mediated using Zn-dust and urea

Method used (conventional)	Solvent-mediated	
	CH ₃ COOH:H ₂ O (1H)	HCl:HNO ₃ (2S)
Reactants	4-nitrophenol	4-nitroaniline
Reagents	Sodium nitrite Sodium azide	Sodium nitrite Sodium azide
Recrystallization	–	Chloroform, ethyl acetate
Extraction	Ether	–
Reaction time	6 h	5 h
Products	4-hydroxyphenyl azide	4-nitrophenyl azide
Physical appearance	Blackish red oil	Yellow orange solid
Yield	85%	92%
Melting point	–	980°C
Boiling point	780°C	–
UV-Vis (hot H ₂ O) λ_{\max} nm	246, 298 nm	222, 322 nm
FTIR (cm ⁻¹)	2,115.91; 2,347.37; 3,334.92; 1,506.41; 1,095.57 cm ⁻¹	2,119.77; 2,258.64; 1,489.05; 812.03; 1,286.52; 3,101.54 cm ⁻¹

Table 4

Comparison of compounds (1L, 2U) through solvent-mediated by using different reactants catalyzed FeCl₃ method

Method used (conventional)	Solvent-mediated	
	DCM	DCM
Reactants	4-hydroxyphenyl azide (1L)	4-nitrophenyl azide (2U)
Reagents	N-bromosuccinimide	N-bromosuccinimide
Recrystallization	Chloroform, ethyl acetate	Chloroform, ethyl acetate
Extraction	Ether	Ether
Reaction time	4 h	3 h
Products	3-bromo-4-hydroxyphenylazide	2-bromo-4-hydroxyphenylazide
Yield	96%	96%
Melting point	287°C	290°C
UV-Vis (hot H ₂ O) λ_{\max} nm	222, 356 nm	288, 342 nm
FTIR (cm ⁻¹)	2,115.91; 2,347.37; 3,323.35; 3,038.38; 1,406.41 cm ⁻¹	2,115.91; 2,347.37; 3,078.39; 1,423.47; 1,296.16 cm ⁻¹
Gas chromatography–mass spectrometry	45, 91, 109, 119, 169, 195, 77, 134, 212 m/z	45, 77, 91, 119, 242 m/z

group adjacent to azide group, aromaticity, C–H stretching, N–O stretching and C–Br.

Mass spectrum (1L) showed that base peak at 45 m/z. Its molecular ion peak came at 212 m/z that is very near to its molecular weight and other peaks such as 42, 134, 105 m/z showed the presence of azide and other fragments. Phenyl group was indicated by the peak at 77 m/z. Thus, all these peaks gave evidence for the synthesis of azides.

Mass Spectrum (2U) showed that base peak at 45 m/z. Its molecular ion peak came at 242 m/z that is very near to its molecular weight and other peaks such as 42, 91, 107 and 119 m/z showed the presence of azide and other fragments. Phenyl group was indicated by the peak at 77 m/z. Thus, all these peaks gave evidence for the synthesis of azides.

3.5. Mass spectral data of all fabricated compounds

Mass fragmentation of synthesized compounds was done with MS Shimidazo QP-2010 spectrophotometer and is shown in Table 5.

Initial and end temperature was set at 50°C and 350°C at every 10°C/min. An electron energy of 70 eV was used by maintaining 10^{-5} torr pressure.

3.6. Solubility

Solubility of synthesized compounds with various solvents is shown in Table 6.

3.7. Comparison of yields of synthesized compounds

- This graph showed the comparison of all synthesized yields that were obtained in good to excellent yield.
- A comparison with the reported data was also shown in Fig. 5.

4. Antibacterial activity of synthesized compounds

All the synthesized compounds were observed their application in biological activity (antibacterial activity) whether they inhibit the growth of bacteria or not. Bacteria are also known as a microscopic organism. Gram staining is the staining technique in which bacteria are divided into gram-negative and gram-positive bacteria. In this procedure, two standard drugs and 4-strains were used.

4.1. Standard drugs

Amoxicillin was applied in one gram-positive bacteria (strain), *Bacillus subtilis* and it showed its inhibition zone in the range of 40 mm. Roxithromycin was applied in three gram-negative bacteria (strains) and they showed their inhibition zone in the range of 30, 22 and 20 mm. These standard

Table 5
Major mass fragment peaks of synthesized compounds

Compounds	Mass fragment peaks	
	Base peak	Molecular ion peak
1I	45	139
1K	45	139
2S	45	167
2T	45	167
1L	45	212
2U	45	242

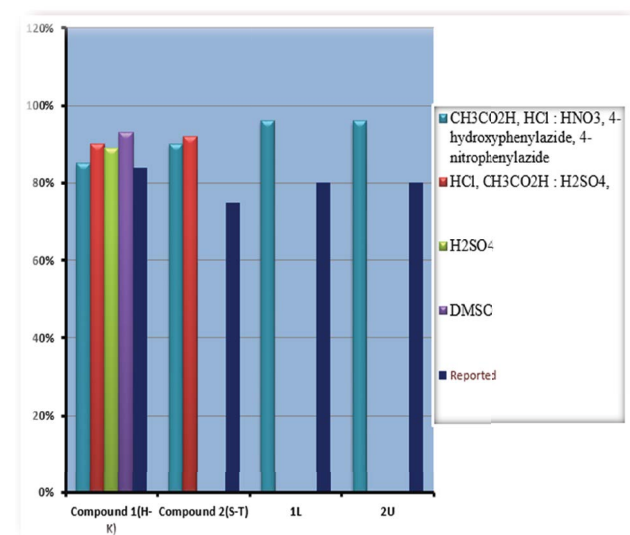


Fig. 5. Comparison of yields of synthesized compounds.

Table 6
Solubility of synthesized compounds

Compounds	Solvents							
	Ethanol	Methanol	Benzene	Ether	Chloroform	n-hexane	DMSO	H ₂ O
1H	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Soluble	Soluble	Insoluble
1I	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Soluble	Soluble	Insoluble
1J	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Soluble	Soluble	Insoluble
1K	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Soluble	Soluble	Insoluble
2S	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Insoluble
2T	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Insoluble
1L	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Insoluble
2U	Soluble	Soluble	Insoluble	Insoluble	Partially	Insoluble	Soluble	Insoluble

Table 7
Antibacterial activity of synthesized compounds

Compounds	Zone of inhibition (mm)			
	Gram-positive		Gram-negative	
	<i>Bacillus subtilis</i>	<i>Pseudomonas aeruginosa</i>	<i>Proteus mirabilis</i>	<i>Agrobacterium tumefaciens</i>
1H	Nil	20	09	18
1I	Nil	12	14	10
1J	Nil	04	17	14
1K	22	12	17	09
2S	24	14	14	12
2T	08	09	10	06
1L	22	07	05	05
2U	Nil	04	12	12
Amoxicillin standard	40	–	–	–
Roxithromycin standard	–	30	20	22

drugs inhibit the growth of bacteria. Antibacterial activity of synthesized compounds is shown in Table 7.

5. Conclusion

This research work provides a specific interest to organic chemists because of the vast applications of substituted azide and their derivatives. The presented study describes the multistep synthesis of 4-hydroxyphenyl azide (85%–93%), 4-nitrophenyl azide with unsaturated sodium azide (90%–92%), 3-bromo-4-hydroxyphenyl azide (85%–92%) and 2-bromo-4-nitrophenyl azide with N-bromosuccinimide (96%). The synthesized compounds have shown remarkable antibacterial activities against all pathogens and K, S, L compounds have inhibited the bacterial growth in the range of (22, 13, 17, 9 mm), (24, 14, 14, 12 mm), (22, 7, 5, 5 mm) against bacterial species (*Bacillus subtilis*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Agrobacterium tumefaciens*) more effectively. Antibacterial activity of synthesized compounds shows that Amoxicillin and Roxithromycin inhibit the growth of bacteria.

We have achieved a good yield of all synthesized compounds with excellent antimicrobial activity (antibacterial activity). The structural elucidation of these compounds was done with UV-Vis, FTIR and mass spectrometry.

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