

Solvent -Free One -Pot Multicomponent, Synthesis, Characterization and Anti-bacterial activity, of some 2-substituted-3-cyano-Pyridine Derivatives

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Abstract

Solvent- free thermal heating, one-pot condensation of acetophenone, ethyl cyanoacetate or malononitrile and substituted Aromatic aldehyde, ammonium acetate give, 2-oxo-3-cyano-4-substituted Aryl-6-phenyl pyridine [I]_{a-h}, or 2-amino-3-cyano-4-substituted Aryl-6-phenyl pyridine derivatives [II]_{a-f}, respectively.

Treatment of compounds 2-oxo-3-cyano-4-substituted Aryl-6-phenyl pyridine with phosphorous penta sulphide (P₂S₅), give 2-thioxo-3-cyano-4-substituted Aryl-6-phenyl pyridine derivatives [III]_{a-c}.

All prepared compounds are characterized by, C.H.N.S- elemental analysis, melting points, FTIR- and ¹H-NMR- spectral analysis.

Antibacterial examination of synthesized compounds [I]_{a-c}, [II]_{a-c} and [III]_{a-c} against five types of, (G-) and (G+) bacterial. in comparison with common antibiotic like Ampicillin, Amoxicilin and Lincomycin the result shows 2-thioxo-3-cyano-4-substituted Aryl-6-phenyl pyridine derivatives are more reactive than 2-oxo-3-cyano pyridine derivatives or 2-amino-3-cyano pyridine derivatives.

Key words: Solvent-free, one-pot, pyridine derivatives.

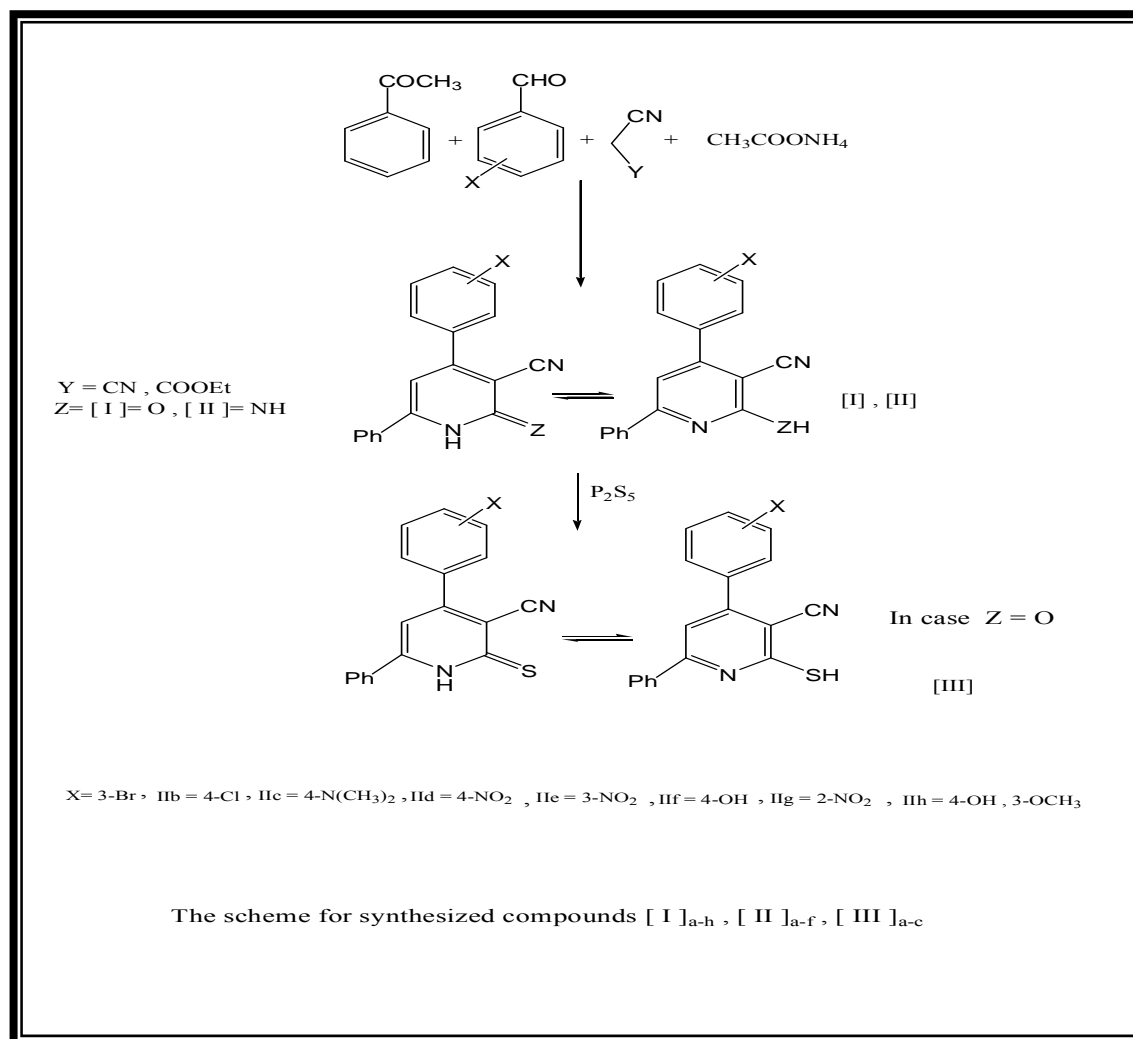
Introduction

One-pot multi-component reactions, is an important synthetic methodology for a broad spectrum of biological and pharmaceutical organic compounds, in which the simultaneous interaction of three or more components in a sequence of steps to afford the final product [1-4].

3-Cyano-2-pyridone derivatives draw a special attention for their wide spectrum biological activities along with their importance and utility as intermediates in preparing variety of heterocyclic compounds [5-7].

In recent years much attention has been developed of 3-cyanopyridine derivatives because of interesting pharmaceutical and biological activities, such as antimicrobial [8-13], analgesic anti-inflammatory [14]; and antitumor agents [15].

In view of the above mentioned facts, and giving attention to the antimicrobial effects of 3-cyanopyridines derivatives, we use the thermal heating solvent-free one-pot multicomponent reaction as a synthetic methodology for synthesis of three different types of 3-cyano pyridine with different substituted in position-2, like 2-oxo-3-cyanopyridine, 2-amino-3-cyanopyridine and 2-thioxo-3-cyanopyridine derivatives, and antibacterial activities examination against five different types of (G-) and (G+) bacteria species .



Experimental

Materials and instruments

All chemicals were supplied from Merck, Fluka and Aldrich Chemicals Co. and used as received.

FTIR spectra were recorded using potassium bromide discs on a Shimadzo (IR prestige-21) FTIR spectrophotometer. ¹H NMR spectra were carried out by company: Bruker, model: ultra shield 400 MHz, origin: Switzerland and are reported in ppm(δ) duterated, DMSO was used as a solvent with TMS as an internal standard. Elemental analysis (C.H.N.S) were carried out using an EuroEA Elemental Analyzer at (The Central Service Laboratory-College of Education For Pure Science Ibn Al-Haitham). Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus. The biological activity was performed in Center for Market Research and Consumer Protection, University of Baghdad.

Synthesis Methods

Synthesis 2-oxo-3-cyano-4-substituted Aryl-6-phenyl pyridine [I]_{a-h}.

A- Solvent-free one-pot multicomponent condensation at 140 °C

A stirred mixture of acetophenone (0.01 mol, 1.17 ml), ethyl cyanoacetate (0.01 mol, 1.1 ml), substituted benzaldehyde (0.01 mol) and ammonium acetate (0.01 mol, 0.77 g) was heated at (140 °C) in oil bath for 15-minute, progress of reaction was monitored by TLC (petroleum ether: ethyl acetate eluent). Dough was formed, solidified upon cooling, then Ethanol was added, a precipitate began to form, left in ice-chest for an hour, then filtered, washed with water and ethanol, dried to give a very good yield (80-90%). Recrystallized from ethanol.

The physical data of these compounds are listed in Table 1. Anal. Calcd. for compound [I]_a C₁₈H₁₁N₂OBr: C, 61.53; H, 3.13; N, 7.97 Found: C, 61.88; H, 3.20; N, 8.21, for Calcd. compound [II]_h C₁₉H₁₄N₂O₃: C, 71.69; H, 4.40; N, 8.80 Found: C, 71.82; H, 4.48; N, 8.86.

B-ethanol reflux one-pot multicomponent condensation of acetophenone, ethyl cyanoacetate, substituted aromatic aldehyde and ammonium acetate for 8 h give poor yield (20-45)% of product.

Synthesis 2-amino-3-cyano-4-substituted Aryl-6-phenyl pyridine [II]_{a-f}.

A-Solvent-free one-pot multicomponent condensation at 140 °C

A stirred mixture of acetophenone (0.01 mol, 1.17 ml), malononitrile (0.01 mol, 0.66 g), substituted benzaldehyde (0.01 mol), and ammonium acetate (0.01 mol, 0.77 g) was heated (140 °C) in oil bath for 20 minute, progress of reaction was monitored by TLC (petroleum ether: ethyl acetate eluent). Dough was formed, solidified upon cooling, then ethanol was added a precipitate began to form, then left in ice-chest for an hour, then filtered, washed with water then ethanol, dried to give a very good yield (75-87%). Recrystallized from ethanol and acetic acid.

B-ethanol reflux one-pot multicomponat condensation of acetophenone, malononitrle, substituted aromatic aldehyde and ammonium acetate for 8 h give poor yield .

The physical data of these compounds are listed in Table 1. Anal. Calcd. For compound [II]_a C₁₈H₁₂N₃Br: C, 61.71; H, 3.42; N, 12.00; Found: C, 61.85 ; H, 3.49; N, 12.28 and Calcd. for compound [II]_b C₁₈H₁₂N₃Cl : C, 70.70 ; H, 3.92; N, 13.74; Found: C,71.11; H,4.01; N, 13.86 .

Synthesis 2- thioxo -3 - cyano -4 -substitued Aryl -6 - phenyl pyridine [III]_{a-c} .

A mixture of 2-oxo3-cyano-4-(x'-substitued phenyl)-6- phenyl -2(*IH*)-pyridinones [II]_{a-c} (0.01 mol) and Phosphorous pentasulphide (P₂S₅) (0.01 mol) in pyridine (10 mL) was refluxed for 5 h . Then reaction mixture was poured into ice-cold water. The separated solid was filtered off and washed with dilute HCl to afford the corresponding thione derivative , which was crystallized from ethanol .

The physical data of these compounds are listed in Table 1. Anal. Calcd. For compound [III]_a C₁₈H₁₁N₂SBr: C,58.85; H, 2.99; N, 7.62; S, 8.71; Found: C, 59.12 ; H, 3.17; N, 7.88; S,8.98 and Calcd. for compound [III]_c C₂₀H₁₇N₃S : C,72.50; H, 5.13; N, 12.68; S, 9.66; Found: C, 72.72 ; H, 5.29; N, 12.92; S,9.90.

Evaluation of Antibacterial Activity

Antibacterial activity of synthesized compounds was determined using a disc diffusion method 30 µl of each Gram negative *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis* and gram positive *Bacillus subtilis*, *Staphylo coccus aureus* bacterial suspension of approximately 10⁸ colony cell/ml was incubated at 37 °C for 24 h, were spread on Muller-Hintone agar using sterile collon. Swaks . 30 mg/ml solution of synthesized compounds in DMSO, were prepared and placed into occulted plates . The plates were incubated aerobically at 37°C for 24 h then inhibition zone diameter (mm) were measured.

Results and Discussion

Thermal-heating one-pot multicomponent condensation of equimolecular amounts of substituted benzaldehyde and acetophenon with ethylcyanoacetate and anhydrous ammonium acetate at 140 °C for less than 15 min ; afforded an excellent yield of 2-oxo- cyanopyridin derivatives [I]_{a-h} (80-90)%. FTIR-spectral analysis of compounds[I]_{a-h}, showed disappearance of carbonyl stretching bands of acetophenone, substituted benzaldehyde, ethyl cyanoacetate ester and ammonium acetate, and appearance of secondary amide carbonyl stretching band (C=O) at 1643-1699cm⁻¹, besides the secondary amide (N-H) stretching bands at 3130-3150cm⁻¹ and cyano stretching bands at 2214-2225cm⁻¹, as well as the appearance of (NO₂) a symmetrical and symmetrical stretching bands of compounds [I]_a 1516 and 1350cm⁻¹ , [I]_e at 1531,1350cm⁻¹ and [I]_g at 1527,1353 cm⁻¹, respectively , while compound [I]_f , [I]_h showed (O-H) stretching band at 3338 and 3429cm⁻¹, respectively. The other data of functional groups which are characteristics of these compounds are given in Table 2.

The ¹HNMR spectrum (in DMSO), of compound [I]_b showed pyridine ring proton at C5 as a singlet signal at 6.82 ppm , aromatic proton (9H) of phenyl groups at C4 and C6 of pyridine ring as a multiplet signal at 7.5-7.9 ppm : equivalent to 9-protons , and secondary amide (N-H) proton as a singlet signal at 12.89 ppm, While ¹HNMR-spectrum of compound [I]_g, showed pyridine ring proton at C5 as a singlet signal at 6.9 ppm , aromatic proton (9H) of phenyl groups at C4 and C6 of pyridine ring as a multiplet signal at 7.5-8.3 ppm : equivalent to 9-protons , and secondary amide (N-H) proton as a singlet signal at 13.0 ppm .

Thermal heating one-pot multicomponent reaction of equimolar amounts of acetophenone, substituted benzaldehyde, malononitrile, ammonium acetate at 140 °C for less than 20 minute give a very good yield (75-87%), with high purity of 2-amino-3-cyano-4(x'-substituted phenyl)-6-phenyl pyridine[II]_{a-f}, which were characterized, (C.H.N.S) elemental analysis, FTIR-spectral analysis and ¹H.NMR-spectral analysis.

The FTIR absorption spectra of compound [II]_a, showed the disappearance of absorption bands of the starting materials together with appearance of (C=N) of pyridine ring at 1610-1643cm⁻¹ and a symmetrical and symmetrical stretching bands of amino group (NH₂) at 3460-3487cm⁻¹ and 3305-3375cm⁻¹, respectively, and cyano group (C≡N) stretching band 2206-2214 cm⁻¹.

Moreover, the ¹HNMR spectrum (in DMSO), of compound [II]_a showed pyridine ring proton at C 5 as a singlet signal at 6.8 ppm, (NH₂) proton as a singlet signal at 6.9 ppm (equivalent to 2-proton) and Aromatic proton (9H) of phenyl groups at C4 and C6 of pyridine ring as a multiplet signal at 7.5-7.7 ppm (equivalent to 9-proton).

Treatment of compounds 2-oxo-3-cyano-4(x'-substituted phenyl)-6-phenyl (2H) pyridine[I]_{a-c} with phosphorous penta sulfide (P₂S₅) in pyridine under reflux give corresponding 2-thioxo-3-cyano-4(x'-substituted phenyl)-6-phenyl (2H) pyridine[III]_{a-c}.

Structure of compounds [III]_{a-c} has been characterized by its melting points, (C.H.N.S) elemental analysis, FTIR and ¹H.NMR-spectral analysis.

FTIR-spectral of compounds [III]_{a-c}, showed disappearance of carbonyl stretching bands of 2-oxo pyridine starting material and appearance of 2-thioxo pyridine (C=S) stretching bands at 1199, 1188, 1184 cm⁻¹, respectively, besides the appearance of secondary thioxo amide (N-H) stretching bands at 3433, 3398, 3394 cm⁻¹, respectively and cyano (C≡N) 2218, 2218, 2210 cm⁻¹, respectively.

¹H.NMR-spectral analysis of compound [III]_a, showed a singlet signal of C5-pyridine ring proton at 7.1 ppm, secondary thioxo amide (N-H) proton at 8.7 ppm, and aromatic proton (9H) of phenyl groups substituted at C4 and C6 of pyridine ring as a multiplet signal at 7.3-8.1 ppm (equivalent to 9-protons). While the ¹H.NMR-spectrum of compound [III]_b, showed C5-pyridine ring proton as singlet signal at 7.1 ppm, secondary thioxo amide (N-H) proton as singlet signal at 8.9 ppm, and aromatic proton (9H) of phenyl groups substituted at C4 and C6 of pyridine ring as a multiplet signal at 7.5-8.0 ppm.

All the spectral data of FTIR spectroscopy of synthesized compounds are listed in Table (2).

Biological Activity

Antibacterial activity of synthesized compounds 2-oxo-3-cyano-4-substituted Aryl-6-phenyl pyridine [I]_{a-c}, 2-amino-3-cyano-4-substituted Aryl-6-phenyl pyridine [II]_{a-c}, 2-thioxo-3-cyano-4-substituted Aryl-6-phenyl pyridine [III]_{a-c} respectively in comparison with common antibiotic, Ampicillin, Amoxicilin and Lincomycin against Gram negative Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis and gram positive Bacillus subtilis, Staphylo coccus aureus. pathogenic species. are given in table (3).

Result showed stronger activity exhibition of compounds [III]_{a-c} against Pseudomonas aeruginosa, Escherichia coli and Staphylo coccus, this may be due to presence of thioxo-group (C=S) at position 2, of 3-cyanopyridine derivatives.

While all synthesized compounds showed stronger activity against Pseudomonas aeruginosa bacteria.

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Table No. (1) Physical properties of synthesized compounds [I]_{a-h}, [II]_{a-f} and [III]_{a-c}

comp. No.	Molecular Formula	M.P C'	Yield% solvent-free At 140 °C	Yield% in ethanol reflux
[II] _a	C ₁₈ H ₁₂ N ₃ Br	240-242	87	25
[II] _b	C ₁₈ H ₁₂ N ₃ Cl	252-253	75	18
[II] _c	C ₂₀ H ₁₈ N ₄	222-224	80	11
[II] _d	C ₁₈ H ₁₂ N ₄ O ₂	230-231	84	14
[II] _e	C ₁₈ H ₁₂ N ₄ O ₂	218-220	80	14
[II] _f	C ₁₈ H ₁₃ N ₃ O	233-235	78	16
[I] _a	C ₁₈ H ₁₁ N ₂ OBr	>300	90	45
[I] _b	C ₁₈ H ₁₁ N ₂ OCl	>300	88	33
[I] _c	C ₂₀ H ₁₇ N ₃ O	>300	83	25
[I] _d	C ₁₈ H ₁₁ N ₃ O ₃	>300	86	28
[I] _e	C ₁₈ H ₁₁ N ₃ O ₃	>300	80	36
[I] _f	C ₁₈ H ₁₂ N ₂ O ₂	>300	85	28
[I] _g	C ₁₈ H ₁₁ N ₃ O ₃	>300	82	20
[I] _h	C ₁₉ H ₁₄ N ₂ O ₃	>300	87	22
[III] _a	C ₁₈ H ₁₁ N ₂ SBr	228-230		
[III] _b	C ₁₈ H ₁₁ N ₂ SCl	238-239		
[III] _c	C ₂₀ H ₁₇ N ₃ S	195-197		

Table No.(2):Characteristic FTIR absorption bands of synthesized compounds [I]_{a-h}, [II]_{a-f} and [III]_{a-c}

Comp. No.	$\nu(\text{N-H})\text{cm}^{-1}$	$\nu(\text{C-H})\text{cm}^{-1}$	$\nu(\text{C}\equiv\text{N})\text{cm}^{-1}$	$\nu(\text{C}=\text{N})\text{cm}^{-1}$	$\nu(\text{C}=\text{O})\text{cm}^{-1}$	$\nu(\text{C}=\text{S})\text{cm}^{-1}$	$\nu(\text{C}=\text{C})\text{cm}^{-1}$
[I] _a	3138	3028- 3055	2214	1608	1643	-	1570-1531
[I] _b	3140	3066-3028	2214	1608	1643	-	1573-1531
[I] _c	3130	3077-3040	2206	1610	1699	-	1564-1517
[I] _d	3150	3062-3020	2210	1608	1674	-	1577-1500
[I] _e	3140	3082-3028	2214	1604	1651	-	1577-1500
[I] _f	3134	3062-3028	2225	1608	1649	-	1575-1519
[I] _g	3148	3077 -3040	2218	1603	1643	-	1519-1502
[I] _h	3136	3066 -3016	2218	1604	1643	-	1573-1525
[II] _a	3358 –3483	3051-3100	2214	1629	-	-	1591-1571
[II] _b	3354 -3480	3037-3003	2214	1643	-	-	1573-1544
[II] _c	3350 -3464	3116-3080	2206	1612	-	-	1566- 1523
[II] _d	3375-3487	3078-3062	2210	1635	-	-	1570 -1554
[II] _e	3305 -3475	3100-3080	2206	1639	-	-	1573- 1550
[II] _f	3311 -3468	3064 -2988	2210	1629	-	-	1571-1544
[III] _a	3433	3080-3055	2218	1608	-	1199	1573-1554
[III] _b	3433	3100-3059	2218	1608	-	1188	1573-1539
[III] _c	3394	3089-3985	2210	1608	-	1184	1573-1554

Table No.(3): Antibacterial activity of synthesized compounds against five pathogenic Species.

Comp. no.	Mean of Inhibition zone Diameter (mm)				
	S. aureus	P.aerugina	E. coli	P. mirabilis	B.subtilis
[I]a	8	27	2	7	4
[I]b	-	10	-	5	3
[I]c	-	22	-	5	3
[II]a	-	20	-	-	-
[II]b	-	26	22	-	-
[II]c	-	17	-	-	-
[III]a	17	28	30	7	4
[III]b	16	6	22	-	-
[III]c	16	22	17	-	-
Ampicillin	5	-	-	-	-
Amoxicilin	15	3	-	-	-
Lincomycin	9	-	-	-	-
Dimethylsulfoxie	0.0	0.0	0.0	0.0	0.0

تخليق (بدون مذيب بوعاء واحد متعدد المكونات) لبعض مشتقات ٢-معوذ-٣-سيانو بريدين ودراسة خواصها البايولوجية وفعاليتها.

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الخلاصة

تكاثف الاسيتوفينون وخالات سيانو اثيل او مالونونايتريل مع الألدهايدات الأروماتية المعوضة وخالات الامونيوم بوعاء واحد وبدون مذيب بالتسخين المباشر عند درجة ١٤٠ م° ليعطي المركبات ٢-اوكسو-٣-سيانو-٤-اريل معوذ-٦-فنيل بريدين [II]_{a-h} ، ٢-امينو-٣-سيانو-٤-اريل معوذ-٦-فنيل بريدين [II]_{a-f} عند معاملة مركبات ٢-اوكسو-٣-سيانو-٤-اريل معوذ-٦-فنيل بريدين [I]_{a-c} مع خامس كبريتيد الفسفور (P₂S₅) ليعطي مركبات ٢-ثايوكسو-٣-سيانو-٤-فنيل معوذ-٦-فنيل بريدين [III]_{a-c}. درست خواص جميع المركبات المحضرة من خلال قياس درجات الانصهارها، تحليل العناصر الدقيق (CHNS) واطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي (FTIR ، ¹H NMR). اظهرت دراسة الفعالية البايولوجية (كمضادات حيوية) للمركبات المحضرة مع خمسة انواع من البكتريا (G-) و (G+) تمت مقارنة الفعالية البايولوجية لهذه المركبات مع المضادات الحيوية الأمبيسلين، الاموكسيلين واللينكوما سين و ان مركبات ٢-ثايوكسو-٣-سيانو-٤-اريل معوذ-٦-فنيل بريدين [III]_{a-c} تمتلك فعالية بايولوجية قوية جدا .

الكلمات المفتاحية: بدون مذيب، بوعاء واحد، مشتقات البريدين.