

Synthesis, Characterization and Antimicrobial Activity of Novel Pyrrolidine-3-carbonitrile Derivatives

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NEWLY synthesized pyrrolidine-3-carbonitrile derivatives were evaluated as antimicrobial activity. The structures of these derivatives were derived from reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (**1**) with the stabilized phosphorus ylides, Wittig-Horner reagents, trialkylphosphites, as well as tris(dialkylamino)phosphines. The antimicrobial activity of the synthesized compounds was evaluated against Gram positive, Gram negative bacteria and fungi. The results showed comparable antibiotic activity to the reference antibiotic compound used in the study.

Keywords: Pyrrolidine, Wittig, Trialkylphosphite, Alkene, Antimicrobial activity.

Introduction

Pyrrolidines are heterocyclic compounds that exhibit wide array of pharmacological activities due to their ability to modulate different biological targets. [1] They possess anti-inflammatory, [2] antitumor,[3] antihistaminic, [4] antihypertensive, [5] antimicrobial, [6] hypnotic, [7] anticonvulsant,[8] antiparkinsonian [9] activities. Among these starting materials for generating diverse pyrrolidine derivatives, pyrrolidinones[10] showed to be attractive ones as they possess both electrophilic and nucleophilic centers enabling them to react with various reagents. 4-cyano-pyrrolidin-3-ones[11,

12] are particularly interesting precursors for synthesis of pyrrolidines. Considering the fact that they have two electrophilic sites, enriches their chemical reactivity and led to generating novel compounds [11], [13–16] of promising biological activity.[16] Based on the literature survey and as a part of our growing interest in preparing new organophosphorus compounds. [17–20] In this article we studied the chemical behavior of 4-cyano-pyrrolidin-3-ones (**1**) towards organophosphorus reagents and evaluation the antimicrobial activity of the products (Fig. 1).

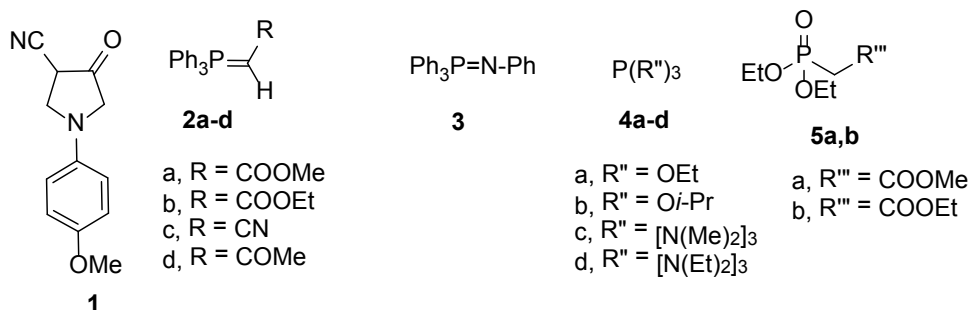


Fig. 1. 4-cyano-pyrrolidin-3-ones (**1**) and organophosphorus reagents.

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Results and Discussion

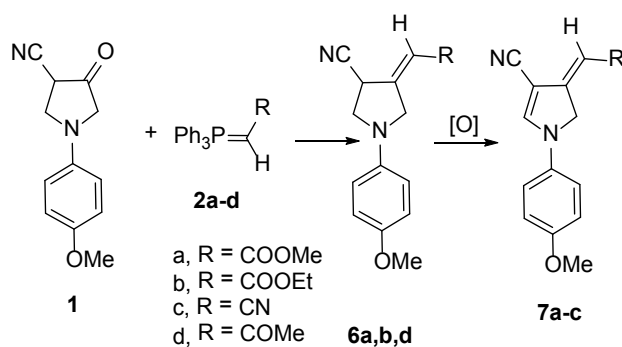
Wittig reaction [21, 22] of 4-cyano-pyrrolidin-3-ones (1) with stabilized ylide 2a-c gave the corresponding unstable olefination products 6a-c. ¹H NMR spectra of products 6a-c showed characteristic proton around 7 ppm indicating trisubstituted alkene formation. Interestingly enough, compounds 6a-c were unstable and they undergo aerobic oxidation[23] to give the corresponding α , β -unsaturated compounds 7a-c as shown in (Scheme 1).

In a similar fashion, reaction of *N*-phenyl triphenylphosphine (3) with ketone 1 gave the corresponding imine via tandem [2+2] cycloaddition–cycloreversion mechanism to provide the oxazaphosphazetidine intermediate [24] that collapses to give the imine which tautomerize to the corresponding enamine 8 (Scheme 2). The structure was assigned based on ¹H NMR peaks at 4.27 and 4.21 ppm for two methylene groups in addition to the IR peak of secondary amine appeared at 3430 cm⁻¹.

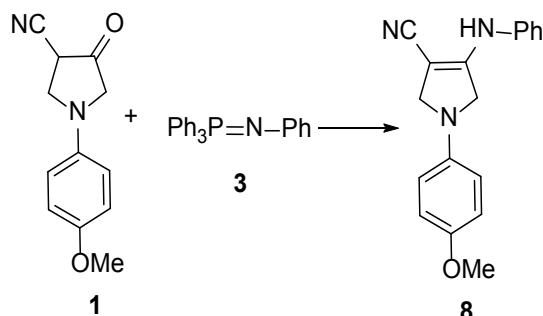
Nucleophilic attack of trialkyl phosphite/phosphorane reagents on ketone 1 proceeds to give the corresponding enol ether compounds 9a,b and enamines 9c,d as shown in Scheme 3. These products were confirmed by spectral data, specifically; ¹H NMR where two methylene signals were detected in the range of 4.0 to 4.4 ppm.

A plausible mechanism of forming products 9a, d is shown in scheme 4. The addition of trialkyl phosphite to the ketone gave intermediate 10 which undergoes nucleophilic attack on the alkyl group on the phosphorus to form compound 11. Deprotonation of compound 11 triggers the elimination of the phosphonate to proceed smoothly to 9a. While in case of trisdiethylaminophosphorane, intramolecular reaction of compound 11' to kick out the alkoxy group followed by elimination to give 9d.

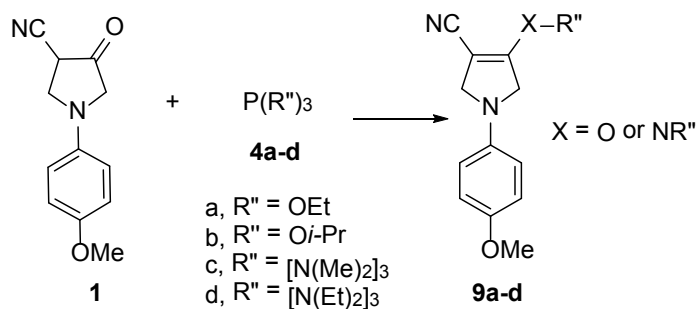
Horner-Wadsworth Emmons reaction [25] of ketone 1 with reagents 5a,b gave the same previously isolated products 7a,b resulted from the reaction of 1 with reagents 2a,b (Scheme 5).



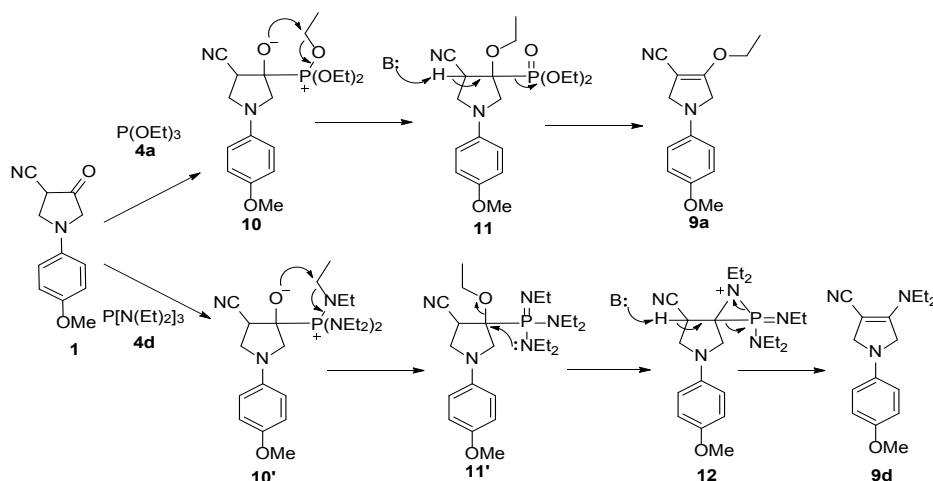
Scheme 1. Reaction of (1) with stabilized yields.



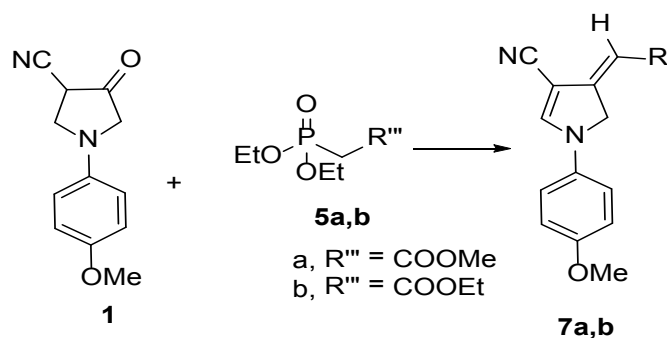
Scheme 2. Reaction of 1 with *N*-phenyl triphenylphosphine (3).



Scheme 3. Reaction of 1 with trialkyl phosphites and trisdialkylaminophosphoranes.



Scheme 4. Proposed mechanism for formation of 9a-d products.



Scheme 5. Horner-Wadsworth Emmons reaction with 1.

Biological evaluation

Antimicrobial activities of seven compounds were investigated against both Gram: *Bacillus subtilis*, *Bacillus cereus*, and *Stephelococcus aureus*, Gram negative: *Escherichia coli*, *Pseudomonas aeruginose*, *Salmonella typhimurium*, and Fungus: *Candida albicans*. The obtained results are compared to the reference antibiotic [Nizo-arm (antifungal) and Cephradine (antimicrobial)] that were purchased from Egyptian markets.

As shown in Table 1 and Fig. 2: The compounds 6d, 7c were found to be highly active compounds against Gram positive: *Stephelococcus aureus* (32 mm inhibition zone) and Gram negative: *Escherichia coli* (20 mm inhibition zone), respectively. These excellent results especially that of 7c, which reaches the bioactivity of the reference antibiotic, enables us to continue the work on this antibacterial substance until reaches application stage in pharmacology studies.

Novel series of pyrrolidine-3-carbonitrile
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TABLE 1. The antibacterial and antifungal activities of some synthesized compounds.

Compound No.	Inhibition zone diameter mm/mg sample						
	Gram +ve bacteria			Gram -ve bacteria			Fungi
	<i>B. cereus</i>	<i>B. subtilis</i>	<i>St. aureus</i>	<i>E. coli</i>	<i>P. aeruginose</i>	<i>Sa. typhimurium</i>	<i>C. albicans</i>
6d	11	4	32	10	8	0.0	2
7a	11	0	0	14	14	10	5
7b	11	2	11	13	11	10	6
7c	11	0	0	20	13	6	6
8	7	0	7	12	12	9	4
9a	7	0	0	9	7	7	1
9c	10	3	0.0	9	0	0.0	4
Reference antibiotic. *	30	40	30	20	50	40	44

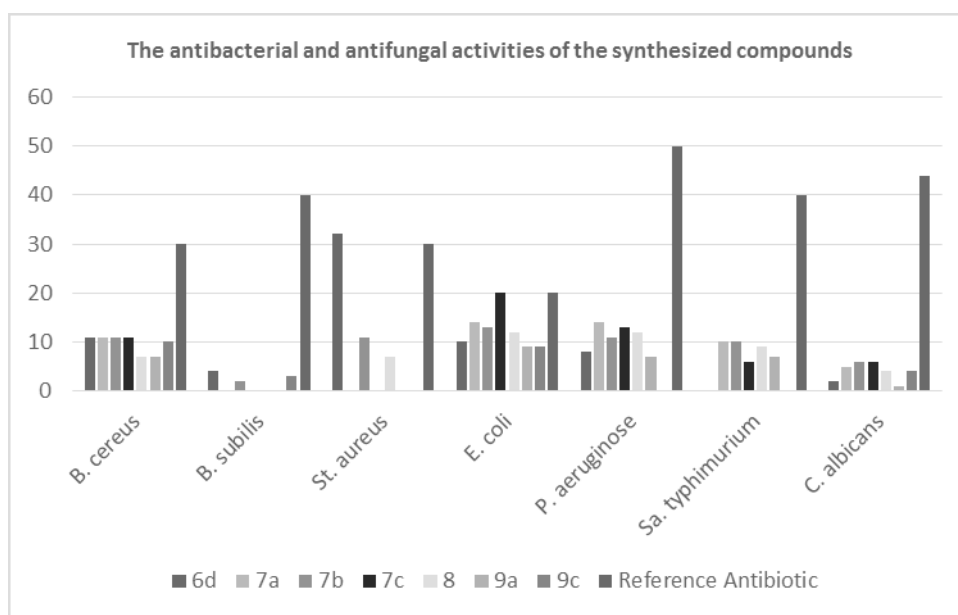


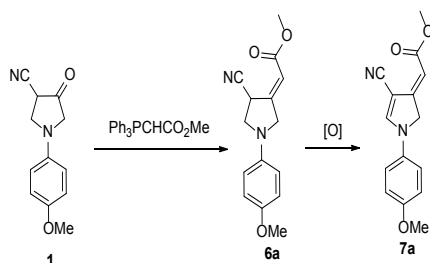
Fig. 2. The antibacterial and antifungal activities of some synthesized compounds.

derivatives was synthesized using different organophosphorus reagents. The antimicrobial activity of these compounds was evaluated against Gram positive, Gram negative bacteria and Fungi. The results showed comparable antibiotic activity to the reference antibiotic compound.

Experimental

Melting points were determined in open glass capillaries using Electrothermal IA 9000 series digital melting point apparatus (Electrothermal, Essex, UK) and are uncorrected. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infracord Spectrophotometer model 157(Grating). The ^1H and ^{13}C NMR spectra were recorded in CDCl_3 or $\text{DMSO}-d_6$ as solvent on JEOL-500 MHz Spectrometer and the chemical shifts were recorded in δ values relative to TMS. The ^{31}P NMR spectra were recorded with a Varian CFT-20 (vs. external 85% H_3PO_4 as a standard). The mass spectra were performed at 70eV on a Shimada GCS-OP 1000 Ex Spectrometer provided with data system. 4-cyano-pyrrolidin-3-one (1) was easily prepared according to the literature.[12]

Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with carbomethoxymethylene triphenylphosphorane (2a).



To a solution of ketone (1) (0.22 g, 1.0 mmol) in dry toluene (30 mL) was added ylide 2a (0.33 g, 1.0 mmol), the mixture was refluxed. After 1 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO_2 , eluting with 3-8% EtOAc in petroleum ether) to afford the unstable alkene (6a, 16%) as a colorless solid followed by conjugated alkene (7a, 73%) as oil.

Methyl(E)-2-(4-cyano-1-(4-methoxyphenyl)pyrrolidin-3-ylidene)acetate (6a)

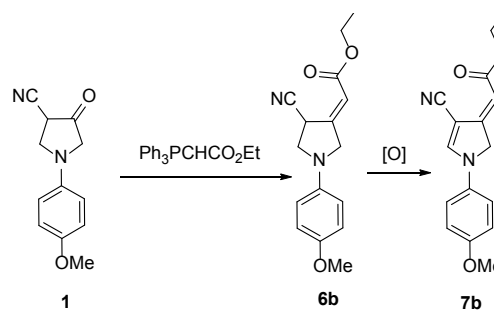
m.p.= 91-93 °C; IR (KBr) 2957, 2216, 1739, 1494, 1354, 1065, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.83-6.96 (m, 3H), 6.44 (d, $J = 7.5$ Hz, 2H), 4.28 (s, 4H), 3.74 (s, 6H), 3.53 (s, 1H);

^{13}C NMR (125 MHz, CDCl_3) δ 168.32, 156.73, 151.43, 142.59, 117.89, 115.67, 115.51, 113.47, 113.31, 112.64, 58.71, 56.04, 51.97, 42.77; MS (EI, 70 eV): m/z (%) = 272 (100%) [M].

Methyl (E)-2-(4-cyano-1-(4-methoxyphenyl)-1,2-dihydro-3H-pyrrol-3-ylidene)acetate (7a)

IR (KBr) 2932, 2203, 1687, 1457, 1312, 1002, 663 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31 (s, 1H), 7.19 (d, $J = 7.4$ Hz, 2H), 6.86-6.90 (m, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 3.57 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ 169.28, 157.93, 132.79, 126.04, 122.64, 119.54, 119.1, 115.32, 114.7, 93.25, 60.7, 55.4, 31.1; MS (EI, 70 eV): m/z (%) = 270 (47%) [M].

Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with carbomethoxymethylene triphenylphosphorane (2b)



To a solution of ketone 1 (0.22 g, 1.0 mmol) in dry toluene (30 mL) was added ylide 2b (0.34 g, 1.0 mmol), the mixture was refluxed. After 1 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO_2 , eluting with 7-15% EtOAc in petroleum ether) to afford the unstable alkene (6b, 12 %) as a colorless solid followed by conjugated alkene (7b, 69%) as oil.

Ethyl (E)-2-(4-cyano-1-(4-methoxyphenyl)pyrrolidin-3-ylidene)acetate (6b)

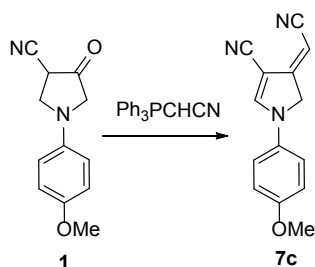
m.p.= 73-76 °C; IR (KBr) 2963, 2219, 1733, 1491, 1344, 1057, 689 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.81-6.92 (m, 3H), 6.42 (d, $J = 7.5$ Hz, 2H), 4.25 (s, 4H), 4.30 (q, $J = 7.0$ Hz, 2H), 3.72 (s, 3H), 3.52 (s, 1H), 1.35. (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.65, 156.35, 150.40, 143.60, 119.90, 115.67, 114.31, 113.31, 111.60, 60.16, 58.71, 56.04, 50.77, 14.70.

Ethyl(E)-2-(4-cyano-1-(4-methoxyphenyl)-1,2-dihydro-3H-pyrrol-3-ylidene)acetate (7b)

IR (KBr) 2932, 2203, 1687, 1457, 1312, 1002, 663 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.34

(d, $J = 2.3$ Hz, 1 H), 7.18 - 7.28 (m, 2 H), 6.89 - 6.98 (m, 3 H), 4.18 (q, $J = 6.9$ Hz, 2 H), 3.81 (s, 3 H), 3.61 (s, 2 H), 1.28 (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 158.8, 132.5, 126.4, 122.7, 120.3, 120.0, 115.4, 114.8, 95.5, 61.1, 55.5, 31.3, 14.1; MS (EI, 70 eV): m/z (%) = 28 ϵ (100%) [M].

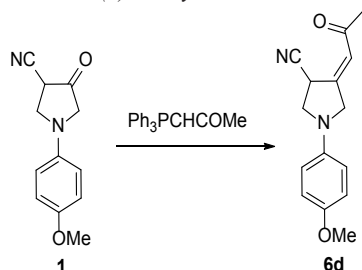
Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with ylide (2c)



(E)-4-(cyanomethylene)-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrrole-3-carbonitrile (7c)

To a solution of ketone 1 (0.22 g, 1.0 mmol) in dry toluene (10 mL) was added ylide 2c (0.31 g, 1.0 mmol), the mixture was refluxed. After 6 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO_2 , eluting with 30 % ethylacetate in petroleum ether) to afford the (7c, 67%) as a colorless solid; m.p. = 152-155 °C; IR (KBr) 3074, 2224, 2217, 1481, 1362, 1091, 714 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ ppm 7.39 (d, $J = 1.2$ Hz, 1 H), 7.24 - 7.28 (m, 2 H), 7.03 - 7.05 (m, 1 H), 6.96 - 6.99 (m, 2 H), 3.84 (s, 3 H), 3.71 (d, $J = 1.2$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.2, 132.0, 127.4, 122.9, 120.2, 116.8, 116.5, 115.0, 114.4, 94.3, 55.6, 14.8; MS (EI, 70 eV): m/z (%) = 237 (68%) [M].

Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with ylide 2d.

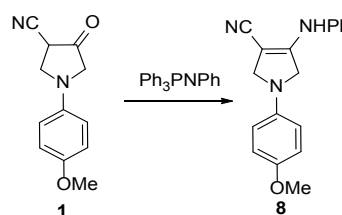


(E)-1-(4-methoxyphenyl)-4-(2-oxopropylidene)pyrrolidine-3-carbonitrile (6d)

To a solution of ketone 1 (0.22 g, 1.0 mmol) in dry toluene (30 mL) was added ylide 2d (0.31 g, 1.0 mmol), the mixture was refluxed. After 6 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO_2 , eluting with 15 % acetone in petroleum ether). *J. Chem.* **61**, No. 3 (2018)

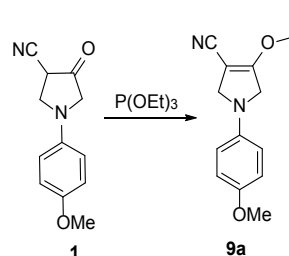
ether) to afford the (6d, 73%) as a colorless solid; m.p. = 136-139 °C; IR (KBr) 3049, 2221, 1617, 1471, 1362, 1094, 703 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.27 (d, $J = 3.3$ Hz, 1 H), 6.87 (d, $J = 9.4$ Hz, 2 H), 6.46 (d, $J = 9.4$ Hz, 2 H), 4.83 (s, 2 H), 4.82 (s, 2 H), 3.77 (s, 3 H), 3.68 (s, 1 H), 3.18 (s, 1 H), 2.30 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 199.44, 151.43, 149.94, 142.59, 124.77, 117.89, 115.67, 113.3, 58.71, 56.04, 50.77, 32.3, 27.47; MS (EI, 70 eV): m/z (%) = 256 (100%) [M].

Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with N-Phenyl triphenylphosphorane (3). 1-(4-methoxyphenyl)-4-(phenylamino)-2,5-dihydro-1H-pyrrole-3-carbonitrile (8)



To a solution of ketone 1 (0.22 g, 1.0 mmol) in dry toluene (30 mL) was added ylide 3 (0.35 g, 1.0 mmol), the mixture was refluxed. After 1 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO_2 , eluting with 7% EtOAc in petroleum ether) to afford the alkene (8, 81%) as a colorless solid; m.p. = 222 -225 °C; IR (KBr) 3430, 2190, 1629, 1039 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.39 - 7.33 (m, 3H), 7.19 (d, $J = 8.1$ Hz, 2H), 6.96 (d, $J = 9.2$ Hz, 2H), 6.47 (d, $J = 9.2$ Hz, 2H), 4.27 (d, $J = 5.4$ Hz, 2H), 4.21 (d, $J = 5.4$ Hz, 2H), 3.81 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.43, 150.37, 142.59, 140.47, 129.18, 129.18, 124.09, 120.92, 120.92, 117.68, 115.67, 115.67, 113.31, 113.31, 60.87, 56.04, 52.94. MS (EI, 70 eV): m/z (%) = 291 (100%) [M].

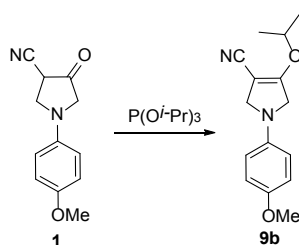
Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with triethylphosphite 4a.



4-ethoxy-1-(4-methoxyphenyl)-2,5-dihydro-1H-pyrrole-3-carbonitrile (9a)

A mixture of ketone 1 (0.22 g, 1.0 mmol) and triethylphosphite (4a) (3 mL), were heated in water bath at 70 °C. After 14 h, the excess triethylphosphite was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, eluting with 30-90 % EtOAc in petroleum ether) to afford the (9a, 61 %) as a colorless solid; m.p.= 161-164 °C; ¹H NMR (500 MHz, CDCl₃) δ 6.82 (d, *J* = 7.5, Hz, 2H), 6.52 (d, *J* = 7.5, Hz, 2H), 4.38 (q, *J* = 6.0 Hz, 2H), 4.18 (s, 2H), 4.15 (s, 2H), 3.65 (s, 3H), 1.31 (t, *J* = 6.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.2, 151.3, 140.8, 114.8, 113.0, 112.2, 76.0, 67.6, 55.3, 53.0, 14.8; ppm; MS (EI, 70 eV): *m/z* (%) = 244 (73%) [M].

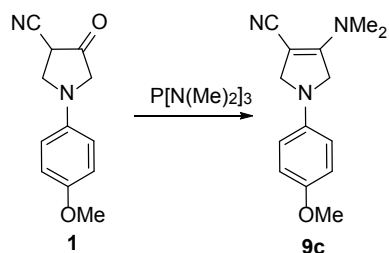
Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with triisopropylphosphite (4b).



4-isopropoxy-1-(4-methoxyphenyl)-2,5-dihydro-1H-pyrrole-3-carbonitrile (9b)

A mixture of ketone 1 (0.22 g, 1.0 mmol) and triisopropylphosphite (4b) (3 mL), were heated in water bath at 70 °C. After 7 h, the excess triethylphosphite was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, eluting with 20-30 % EtOAc in petroleum ether) to afford the (9b, 53 %) as a colorless solid; m.p.= 183-184 °C; ¹H NMR (500 MHz, CDCl₃) δ ppm 6.93 - 7.02 (m, 2 H), 6.48 - 6.63 (m, 2 H), 5.19 (dt, *J* = 12.0, 6.0 Hz, 1 H), 4.33 (t, *J* = 4.3 Hz, 2 H), 4.18 (t, *J* = 4.3 Hz, 2 H), 3.87 (s, 3 H), 1.54 (s, 3 H), 1.52 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 164.6, 151.9, 140.7, 122.4, 115.1, 112.1, 75.5, 74.9, 55.8, 54.9, 22.4ppm; MS (EI, 70 eV): *m/z* (%) = 258 (93%) [M].

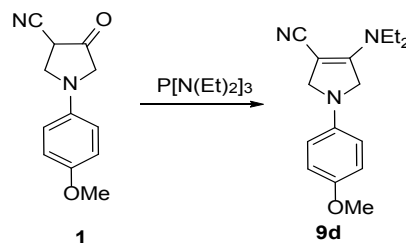
Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with trisdimethylaminophosphorane (4c).



4-(dimethylamino)-1-(4-methoxyphenyl)-2,5-dihydro-1H-pyrrole-3-carbonitrile (9c)

To a solution of ketone 1 (0.22 g, 1.0 mmol) in dry toluene (30 mL) was added trisdimethylaminophosphorane 4c (0.16 g, 1.0 mmol), the mixture was refluxed. After 8 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, eluting with 7% EtOAc in petroleum ether) to afford the (9c, 48 %) as a colorless solid; m.p.= 163-165 °C. ¹H NMR (500 MHz, CDCl₃) δ 6.68 (d, *J* = 9.3 Hz, 2H), 6.38 (d, *J* = 9.3 Hz, 2H), 4.02 (s, 2H), 4.01 (s, 2H), 4.15 (s, 1H), 3.52 (s, 3H), 2.94 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 157.4, 151.3, 141.2, 119.9, 115.0, 112.5, 64.0, 55.5, 55.0, 54.8, 39.7; MS (EI, 70 eV): *m/z* (%) = 242 (49%) [M]⁺.

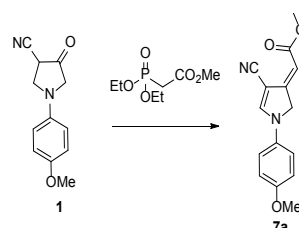
Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile (1) with trisdiethylaminophosphorane (4d).



4-(diethylamino)-1-(4-methoxyphenyl)-2,5-dihydro-1H-pyrrole-3-carbonitrile (9d)

To a solution of ketone 1 (0.22 g, 1.0 mmol) in dry toluene (30 mL) was added trisdiethylaminophosphorane 4d (0.25 g, 1.0 mmol), the mixture was refluxed. After 7 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, eluting with 30% EtOAc in petroleum ether) to afford the (9d, 44 %) as a colorless solid; m.p.= 141-143 °C. ¹H NMR (500 MHz, CDCl₃) δ 6.81 (d, *J* = 9.9, 2H), 6.53 (d, *J* = 9.9, 2H), 4.19 (s, 2H), 4.08 (s, 2H), 3.65 (s, 3H), 3.37 (q, *J* = 8.2 Hz, 2H), 1.16 (t, *J* = 8.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.9, 151.1, 141.0, 119.3, 114.7, 112.4, 62.3, 55.3, 54.7, 54.3, 44.7, 13.9 ; MS (EI, 70 eV): *m/z* (%) = 271 (100%) [M].

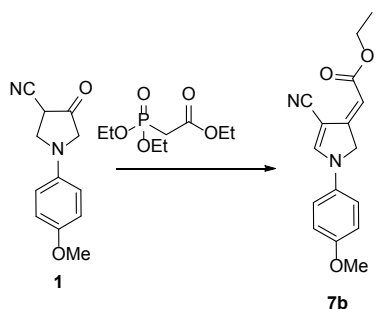
Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile with 5a.



Methyl(E)-2-(4-cyano-1-(4-methoxyphenyl)-1,2-dihydro-3H-pyrrol-3-ylidene)acetate(7a)

To a solution of ketone 1 (0.22 g, 1.0 mmol) in absolute ethanol (30 mL) was added Hornor reagent 5a (0.21 g, 1.0 mmol), followed by few drops of piperidine, the mixture was stirred. After 8 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, eluting with 3-8% EtOAc in petroleum ether) to afford (7a, 79 %) as a colorless oil.

Reactions of 1-(4-methoxyphenyl)-4-oxopyrrolidine-3-carbonitrile with 5b.



Ethyl (E)-2-(4-cyano-1-(4-methoxyphenyl)-1,2-dihydro-3H-pyrrol-3-ylidene)acetate (7b)

To a solution of ketone 1 (0.22 g, 1.0 mmol) in absolute ethanol (30 mL) was added Hornor reagent 5b (0.22 g, 1.0 mmol), followed by few drops of piperidine, the mixture was stirred. After 7 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, eluting with 7-15% EtOAc in petroleum ether) to afford (7b, 77 %) as a colorless oil.

Biological Screening

The antibacterial and antifungal activities were carried out in the Microbial Chemistry Department, National Research Centre, using the diffusion plate method. [27–30]

Procedure

A disc of sterilized filter paper saturated with measured quantity (25 μ L) of the tested sample (1 mg/mL final concentration) was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) or a fungal medium (Dox's medium) which has been seeded with the spore suspension of the test organism. After incubation at 37 °C for 24 h for bacteria (in case of fungi, at 25 °C for 72 h), the diameter of the clear zone of inhibition surrounding the sample was taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter \times 100). All measurements were done in chloroform *Egypt. J. Chem.* **61**, No. 3 (2018)

as a solvent except substance 8 which is dissolved in alcohol.

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تشبيد و اثبات التركيب الكيميائي و دراسة النشاط الميكروبي لمشتقات جديدة لمركبات البيروولدين-3-نيتريل

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تشبيد مشتقات جديدة من مركبات البيروولدين من خلال تفاعل مركب البيروولدينون 1 مع الكواشف الفسفورية المختلفة مثل كواشف فيتج و هورنر الى جانب الفوسفينات ثلاثيه الالكيل و الفوسفينات الامينية و تقييم تلك المركبات مضادات حيوية و مضادات للفطريات. اظهرت نتائج هذه الدراسة ان فاعليته بعض المركبات المشيده تصل لدرجة متقاربه للمضاد الحيوى التجارى المستخدم فى الدراسة.