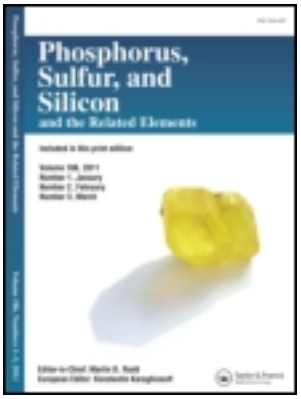

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Synthesis of a Series of Diphenyl (Arylamino)(Pyridin-3-yl)Methylphosphonates as Potential Antimicrobial Agents

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SYNTHESIS OF A SERIES OF DIPHENYL (ARYLAMINO)(PYRIDIN-3-YL)METHYLPHOSPHONATES AS POTENTIAL ANTIMICROBIAL AGENTS

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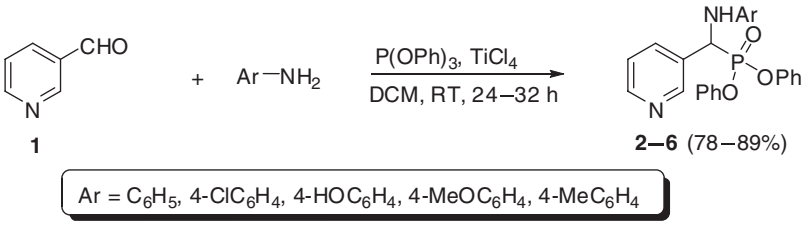
GRAPHICAL ABSTRACT



Abstract *Diphenyl 1-(arylamino)(pyridin-3-yl)methylphosphonates were obtained in high yields from the reactions of nicotinaldehyde with aromatic amines and triphenylphosphite in the presence of titanium tetrachloride ($TiCl_4$) as a catalyst. The structures of the synthesized compounds were confirmed by IR, ^1H NMR and mass spectral data and their purities were confirmed by elemental analyses. The synthesized α-aminophosphonates showed moderate to high antimicrobial activities against Escherichia coli (NCIM2065) as a Gram-negative bacterium, Bacillus subtilis (PC1219) and Staphylococcus aureus (ATCC25292) as Gram-positive bacteria, and Candida albicans and Schccaromycies cerevisiae as fungi, at various concentrations (10–100 μg/mL).The lethal dose of the synthesized compounds was also determined and indicated that most compounds are safe to use.*

Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the related elements *to view the free supplemental file.*

Keywords α-Aminophosphonate; nicotinaldehyde; minimum inhibitory concentrations; antimicrobial properties; lethal dose

INTRODUCTION

Heterocyclic compounds containing nitrogen play an important role in medicinal chemistry and have been intensively used in drug development.[1] The pyridine moiety

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has been found in various biologically active compounds, natural products, and pharmaceuticals.[2–4] On the other hand, various synthetic processes have been developed for the production of α−aminophosphonates.[5–7] However, the most efficient method involves a one-pot Mannich-type[8] process of carbonyl compounds, amines, and diphenyl phosphite in the presence of a Lewis acid catalyst. Such process is high yielding, general, simple, and accommodates various substituents into α-aminophosphonates.[9–12]

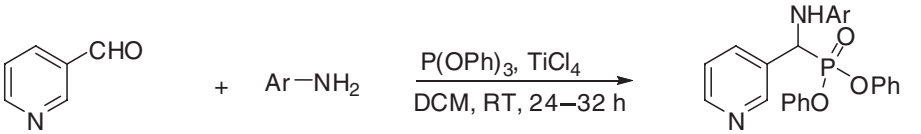
α-Aminophosphonates, and in particular the ones having heterocyclic moieties, show very interesting biological activities[13–15] and have been used as antibacterial,[16,17] antifungal,[16,17] anticancer,[18–20] anti-HIV enzyme inhibitors,[16] antibiotics,[5] and herbicidal agents.[13] Therefore, the synthesis of α-aminophosphonates having a pyridine moiety in an attempt to improve the biological activities of the synthesized compounds is always of interest.

We have developed simple and efficient synthetic procedures for the syntheses of a range of biologically active heterocyclic compounds[21–29] as part of our continuing work in organic synthesis.[30–37] Recently, we have shown that various novel α-aminophosphonates can be produced efficiently, in high yields in a one-step reaction, and such compounds have proven to be good antimicrobial and anticancer reagents.[38–40] The present work was aimed to synthesize a series of α-aminophosphonates containing pyridine moiety with the hope that new antimicrobial agents could be developed. We now report the successful synthesis of a range of diphenyl (arylamino)(pyridin-3-yl)methylphosphonates and their antimicrobial properties.

RESULTS AND DISCUSSION

Chemistry

The reactions of nicotinaldehyde (**1**; 2 mol equiv.) with arylamines (aniline, 4-chloroaniline, 4-hydroxyaniline, 4-anisidine, and 4-toluidine; 4 mol equiv.) and triphenylphosphite (3 mol equiv.) in the presence of titanium tetrachloride ($TiCl_4$), as a Lewis acid, were carried out in dichloromethane (DCM) at room temperature (r.t.) for 24–32 h under identical conditions. The crude products obtained were purified by crystallization from ethanol to give the corresponding α-aminophosphonates **2**–**6** (Scheme 1) in 78–89% yields. The reaction represented in Scheme 1 is general, simple, high yielding, involves easy work-up, and accommodates various substituents to produce substituted α-aminophosphonates efficiently.



1 Ar = C_6H_5, 4-ClC_6H_4, 4-HOC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4 **2–6**

Scheme 1

The structures of α-aminophosphonates **2**–**6** were confirmed by IR, ^{1}H NMR, and mass spectroscopy and their purities were confirmed by elemental analyses. The IR spectra of **2**–**6** are characterized by the presence of absorption bands within the 3424–3305 cm^{-1} region corresponding to the stretching vibrations of the NH groups. The bands within the 1599−1582 cm^{-1} region are due to the stretching vibration of the C=N groups of

the pyridine ring while the absorption bands at the 1361–1320 cm^{-1} region are due to the symmetric stretching vibrations of the P=O groups and absorption bands within the 869–801 cm^{-1} region are attributed to the P–O–C groups.

The ^1H NMR spectra of α-aminophosphonates **2–6** showed a characteristic exchangeable singlet within the 9.68–8.88 ppm region due to the NH protons while the CH protons resonated as doublets (J = 13–16 Hz) within the 6.56–4.85 ppm region. The structures of **2–6** were also confirmed by low-resolution mass spectra and the molecular or pseudomolecular ions were confirmed by the high-resolution mass spectra. Moreover, the elemental analyses of compounds **2–6** were consistent with the suggested structures (see Experimental section for details).

Antimicrobial Activities

α-Aminophosphonates **2–6** were screened for their in vitro antibacterial and antifungal activities against *Escherichia coli (NCIM2065)* as a Gram-negative bacterium, *Bacillus subtilis (PC1219)* and *Staphylococcus aureus (ATCC25292)* as Gram-positive bacteria, and *Schccaromycies cerevisiae* and *Candida albicans* as fungi. The inhibition zones were measured in triplicates and the results are reported in Table S1 in the Supplemental Materials (posted online only).

The results showed that compounds **2–6** showed moderate to high antimicrobial activities against the tested organisms. It was found that compound **4** was the most effective while compound **5** was the least active one.

Minimum Inhibitory Concentrations

The inhibition zone was measured in triplicates in four different concentrations (10–1000 μg/mL) and the mean value ± standard deviation (SD) is recorded in Table S2 in the Supplemental Materials (posted online only). It is clear that compound **6** showed the highest antimicrobial activities at low concentration (10 μg/mL). The compounds could be arranged according to their minimum inhibitory concentration (MIC) as follows: **6** > **3**, **4** > **2** > **5**.

The Lethal Dose

Cytotoxic anticancer substances have unique problems that come primarily from the lack of safety and side effects. Therefore, the cytotoxicity lethal dose (LD_{50}) of α-aminophosphonates **2–6** was determined to the larvae of *Artemia salina* using brine shrimp lethality bioassay. The LD_{50} of compounds **2–6** are represented in Figures S1−S5 in the Supplemental Materials (posted online only).

α-Aminophosphonates **2**−**6** showed low toxicity and they are safe to be used in vivo. Moreover, α-aminophosphonates **2**, **3**, and **6** were found to be safe for use because they exhibited high values of lethal dose. On the other hand, α-aminophosphonates **4** and **5** exhibited small values of lethal dose.

CONCLUSIONS

A convenient method for the synthesis of diphenyl 1-(arylamino)(pyridin-3-yl)methylphosphonates was developed. The synthesized compounds exhibit a remarkable

inhibition of the growth of Gram-positive, Gram-negative bacteria, and fungi at relatively low concentrations. The lethal dose of the synthesized compounds indicated that most of the synthesized compounds are safe and are promising for their uses as in vivo antimicrobial reagents.

EXPERIMENTAL

General Experimental. Melting point determinations were performed by the open capillary method using an electrothermal MEL–TEMP II apparatus, at Tanta, Egypt, and are reported uncorrected. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer, at Tanta, Egypt, using the KBr disc technique. The ^{1}H NMR spectra were recorded on a Bruker AC400 spectrometer operating at 400 MHz at Tanta, Egypt. The ^{31}P NMR spectra were recorded on a Bruker AC500 spectrometer operating at 202.48 MHz at Cardiff, UK. The spectra were recorded in DMSO-d_6. Chemical shifts δ are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Assignments of signals are based on integration values and expected chemical shift values and have not been rigorously confirmed. Low-resolution mass spectra were recorded on a Waters GCT Premier spectrometer, at Cardiff, UK, and high-resolution mass spectra were recorded on a Waters LCT Premier XE instrument at Cardiff, UK. Microanalysis was performed by analytical service at both the Universities of Tanta and Cairo, Egypt. Analytical thin layer chromatography (TLC) was performed on EM silica gel F_{254} sheet (0.2 mm) with petroleum ether (40–60 °C)/acetone (5:2 by volume) as a developing eluent. The spots were detected with UV Lamp Model UV GL-58. Reagents and solvents were obtained from commercial sources and used without purification.

Chemistry

General Procedure for the Synthesis of Diphenyl (arylamino)(pyridin-3-yl)methylphosphonates (2–6). A mixture of **1** (1.07 g, 10.0 mmol), aromatic amine (20.0 mmol), triphenylphosphite (4.65 g, 15.0 mmol), and titanium tetrachloride ($TiCl_4$; 0.19 g; 1.0 mmol) in DCM (10 mL) was stirred at r.t. for 24–32 h during which the progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue obtained was treated with methanol (20 mL), and then filtered to remove the solid materials. A mixture of water (10 mL) and DCM (20 mL) was added to the filtrate, and the organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which recrystallized from ethanol to give the pure products **2–6** as white solids. The ^{1}H and ^{31}P NMR spectra for compound **2** are presented as Figures S6 and S7 in the Supplemental Materials (posted online only).

Diphenyl (phenylamino)(pyridin-3-yl)methylphosphonate (2). Reaction time: 24 h; Yield: 81%; mp: 112−114 °C. Selected IR data (KBr): 3390 (NH), 1596 (C=N), 1320 (P=O), and 823 (P–O–C) cm^{-1}. ^{1}H NMR (MeCOMe/DMSO-d_6): δ 8.44–6.18 (m, 20 H, Ar–H, and NH) and 5.25 (2 d, J = 11 Hz, 1 H, CH) ppm. ^{31}P NMR (DMSO-d_6): δ 16.0 ppm. AP^{+}–MS: *m/z* (%) 418 ([M + 2 H]$^{+}$, 28), 417 ([M + H]$^{+}$, 100), 368 (4), 327 (12), 269 (18), 229 (51), and 199 (15). HRMS (AP^{+}): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{22}N_2O_3P$: 417.1368; found: 417.1351. Anal calcd for $C_{24}H_{21}N_2O_3P$ (416.41): C, 69.22; H, 5.08; N, 6.73; P, 7.44. Found: C, 69.25; H, 5.10; N, 6.74; P, 7.35.

Diphenyl (4-chlorophenylamino)(pyridin-3-yl)methylphosphonate (3). Reaction time: 28 h; Yield: 78%; mp: 135−137 °C. Selected IR data (KBr): 3305 (NH), 1588 (C=N), 1361 (P=O), and 820 (P–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.88–6.97 (m, 19 H, Ar–H, and NH) and 5.75 (2 d, $J = 13$ Hz, 1 H, CH) ppm. ^{31}P NMR (DMSO-d_6): δ 16.1 pm. AP^+–MS: *m/z* (%) 453 ($[M^{37}Cl + H]^+$, 33), 451 ($[M^{35}Cl + H]^+$, 100), 417 (12), 385 (27), 368 (30), 327 (32), and 249 (11). HRMS (AP^+): *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}{}^{35}ClN_2O_3P$: 451.0978; found: 451.0963. Anal calcd for $C_{24}H_{20}ClN_2O_3P$ (450.85): C, 63.94; H, 4.47; N, 6.21; P, 6.87. Found: C, 64.20; H, 4.21; N, 6.16; P, 6.85.

Diphenyl (4-hydroxyphenylamino)(pyridin-3-yl)methylphosphonate (4). Reaction time: 24 h; Yield: 81%; mp: 205−207 °C. Selected IR data (KBr): 3424 (NH/OH), 1585 (C=N), 1334 (P=O), and 869 (P–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.90–6.93 (m, 20 H, Ar–H, OH, and NH) and 5.73 (2 d, $J = 15$ Hz, 1 H, CH) ppm. ^{31}P NMR (DMSO-d_6): δ 15.1 ppm. EI–MS: *m/z* (%) 433 ($[M + H]^+$, 4), 432 (M^+, 16), 339 (26), 246 (66), and 199 (100). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{24}H_{21}N_2O_4P$: 432.1239; found: 432.1241. Anal calcd for $C_{24}H_{21}N_2O_4P$ (432.41): C, 66.66; H, 4.90; N, 6.48; P, 7.16. Found: C, 66.70; H, 4.92; N, 6.45; P, 7.15.

Diphenyl (4-methoxyphenylamino)(pyridin-3-yl)methylphosphonate (5). Reaction time: 30 h; Yield: 88%; mp: 160−162 °C. Selected IR data (KBr): 3422 (NH), 1582 (C=N), 1325 (P=O), and 801 (P–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.93–6.71 (m, 19 H, Ar–H, and NH); 5.69 (2 d, $J = 16$ Hz, 1 H, CH); and 4.17 (s, 3 H, OCH_3) ppm. ^{31}P NMR (DMSO-d_6): δ 15.1 ppm. AP^+–MS: *m/z* (%) 447 ($[M + H]^+$, 3), 415 (2), 294 (5), 193 (6), 140 (8), 117 (22), 100 (100), 97 (57), and 77 (47). HRMS (AP^+): *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}N_2O_4P$: 447.1474; found: 447.1478. Anal calcd for $C_{25}H_{23}N_2O_4P$ (446.43): C, 67.26; H, 5.19; N, 6.27; P, 6.94. Found: C, 67.22; H, 5.02; N, 6.57; P, 6.90.

Diphenyl (4-methylphenylamino)(pyridin-3-yl)methylphosphonate (6). Reaction time: 32 h; Yield: 89%; mp: 194−196 °C. Selected IR data (KBr): 3391 (NH), 1599 (C=N), 1343 (P=O), and 836 (P–O–C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.73–6.66 (m, 19 H, Ar–H, and NH); 4.85 (2 d, $J = 14$ Hz, 1 H, CH); and 2.29 (s, 3 H, CH_3) ppm. ^{31}P NMR (DMSO-d_6): δ 16.1 ppm. AP^+–MS: *m/z* (%) 472 ($[M + MeCNH]^+$, 9), 432 ($[M + 2\ H]^+$, 25), 431 ($[M + H]^+$, 100), 368 (12), 327 (17), and 294 (6). HRMS (AP^+): *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}N_2O_3P$: 431.1525; found: 431.1506. Anal calcd for $C_{25}H_{23}N_2O_3P$ (430.43): C, 69.76; H, 5.39; N, 6.51; P, 7.20. Found: C, 69.72; H, 5.34; N, 6.48; P, 7.15.

Biological Assay

Gram-Negative Bacteria. After Gram-staining procedure, Gram-negative cells appear pink. The Gram-negative bacterium used in this study was *E. coli*, which is known as the backbone for Gram-negative bacteria and causes urinary infection, wound infection, and gastroenteritis.

Gram-Positive Bacteria. The thick cell wall of a Gram-positive organism retains the crystal violet dye used in the Gram-staining procedure, so the stained cells appear purple under magnification. Gram-positive bacteria used in this study were *B. subtilis (PC1219)* and *S. aureus (ATCC25292)*. *B. subtilis* are mostly involved in urinary infection, wound, ulceration, and septicemia. *S. aureus* is the milestone of Gram-positive bacteria and is a causative agent of pneumonia, meningitis, and food poisoning.

Fungi. Pathogenic fungi, especially yeasts, are responsible for a number of diseases in humans, animals. A number of pathogenic strains of fungi are represented in *C. albicans* and *S. cerevisiae*. The tested organisms were obtained from the culture collection

of Bacteriology Unit, Department of Botany, Faculty of Science, Tanta University, Tanta, Egypt.

Determination of Minimum Inhibitory Concentrations. The antimicrobial activities of the tested samples were determined by measuring the diameter of zone of inhibition expressed in millimeters. The inhibition zones were measured in triplicates and expressed as mean ± SD.[42]

The Lethal Dose. Brine shrimps lethality bioassay is very simple bench-top assay used to measure cytotoxicity of plant extracts as well as the synthesized compounds. Three replicates were used for each concentration and living larvae were counted after 72 h. All data were expressed as mean ± SD.[43]

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