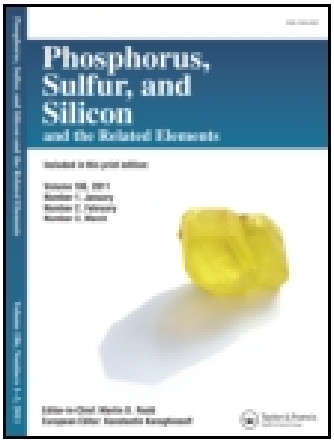

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Nano-$BF_3.SiO_2$ Catalyst-Promoted Michaelis-Arbuzov Reaction: Solvent-Free Synthesis and Antimicrobial Evaluation

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NANO-$BF_3.SiO_2$ CATALYST-PROMOTED MICHAELIS-ARBUZOV REACTION: SOLVENT-FREE SYNTHESIS AND ANTIMICROBIAL EVALUATION

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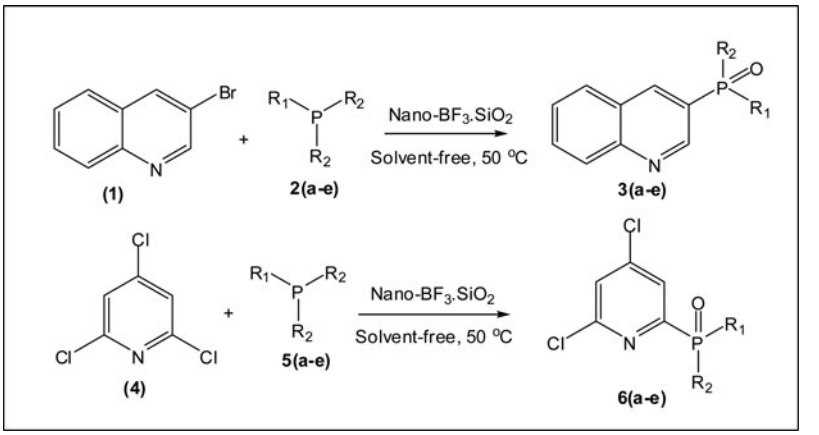
GRAPHICAL ABSTRACT



Abstract *A simple, convenient synthetic route for the synthesis of novel dialkyl heteroaryl phosphonates by a reusable and green nano-$BF_3.SiO_2$ solid catalyst under solvent-free conditions through Michaelis–Arbuzov reaction with high yields is presented. All the newly synthesized compounds were characterized by spectral data and screened for their antimicrobial activity. Some of the compounds exhibited potent antibacterial activity against all the tested pathogens, and warrant further investigation.*

Keywords Michaelis–Arbuzov reaction; nano-$BF_3.SiO_2$; antimicrobial activity; multidrug resistant activity (MDR); organophosphorus compounds; phosphonates

INTRODUCTION

Organophosphorus compounds bearing a phosphorus-carbon bond have played a key role in numerous biologically active compounds, but the occurrences of these compounds

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are not widespread in nature. Phosphonates have a broad range of applications in various fields such as medicinal and synthetic chemistry. Phosphonates represent a group of stable organophosphorus compounds comprising a single P-C bond which makes their molecules resistant to chemical and enzymatic hydrolysis, thermal decomposition,[1] photolysis,[2] and inhibitors for certain biosynthetic pathways[3] and they are widely used as flame retardants, herbicides, detergents, pesticides, chelating agents for di- and trivalent metal ions, and reagents for Wittig–Horner reactions.[4-9] Arylmethyl and heteroarylmethyl phosphonate compounds have been widely utilized as prominent precursors for the synthesis of stilbene dendrimers[10] and optical materials like alkyl(phenylvinylenes),[11] trialkylamine-tethered vinylenes,[12] and thienylvinylenes.[13]

The Michaelis–Arbuzov reaction is considered as an efficient fundamental reaction for the preparation of alkyl/aryl phosphonates from alkyl/aryl halides and trialkyl/aryl phosphites.[14] However, the reaction has some drawbacks such as the need for elevated temperature, removal of the trialkyl phosphites used in excess, and weaker electrophiles aryl/heteroaryl halides or vinyl halides that give lower yields. To avoid these problems, researchers have been focusing considerable attention to enhance the efficiency of the reaction by using new catalysts.

Various reports were found in the literature for the formation of a C—P bond with different catalysts such as iodine,[15] $BF_3.OEt_2$,[16] $NiCl_2$,[17] $Pd(OAc)_2$,[18] $CeCl_3.7H_2O$,[19] and ionic liquids[20] through Michaelis–Arbuzov reaction. There are some drawbacks using the above mentioned catalysts. $BF_3.OEt_2$ requires longer reaction time, low yields, lack of generality, and requires stoichiometric amount of the toxic and moisture sensitive catalyst. $NiCl_2$ and $Pd(OAc)_2$ require vigorous conditions such as high temperature for completion of the reaction. In order to avoid the above-mentioned problems and to enhance efficiency of the reaction we tested $BF_3.SiO_2$[22-24] and nano BF_3-SiO_2[21] catalysts to synthesize the dialkyl heteroaryl phosphonates.

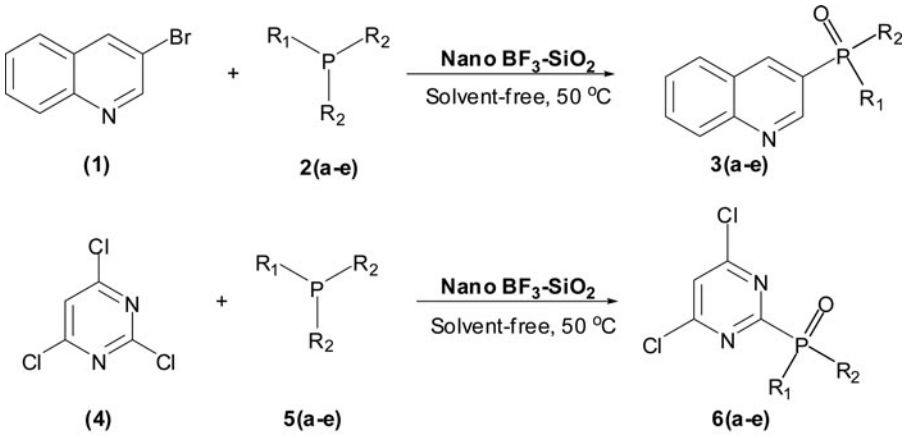
Because of the broad range of applications of phosphonates in medicinal and synthetic chemistry, we focused on designing new active phosphonate molecules and the development of new methodologies for their synthesis in a simple and cost effective manner under solvent-free conditions.

RESULTS AND DISCUSSION

Chemistry

The synthesis of dialkyl heteroaryl phosphonate **3(a–e)** and **6(a–e)** derivatives was carried out effectively in the presence of nano-$BF_3.SiO_2$ under solvent-free conditions as represented in Scheme 1.

3-Bromoquinoline **(1)** and triethylphosphite **(2b)** were selected as models for optimizing the reaction conditions. The model reaction was carried out in different solvents like acetonitrile (ACN), dichloromethane (DCM), toluene, methanol (MeOH), 1,4-dioxane, dimethyl formamide (DMF) and in solvent-free conditions in the presence of $BF_3.SiO_2$ and nano-$BF_3.SiO_2$ catalysts to synthesize compound **(3b)** and the yield is shown in Table 1. The optimum yield of the product was observed when the reaction progressed under solvent-free conditions. Also, the temperature effect, the amount of the catalyst and the reusability of the catalyst up to five cycles were examined, revealing that the reaction was effectively progressed at 50 °C in the presence of 20 mol% nano-$BF_3.SiO_2$ catalyst and no significant diminishing of the catalytic action on the reaction was observed until the catalyst had been reused three times. After optimization of the reaction



Compounds	R_1	R_2
3a, 6a	OMe	OMe
3b, 6b	OEt	OEt
3c, 6c	O*i*-Pr	O*i*-Pr
3d, 6d	OBut	OBut
3e, 6e	Ph	OMe

Scheme 1 Synthesis of dialkyl heteroaryl phosphonates **3(a–e)** and **6(a–e)**.

conditions, the generality of the reaction was checked by altering heteroaryl halides and tri alkylphosphites.

Structures of the newly synthesized compounds **3(a–e)** and **6(a–e)** were confirmed by IR, ^{1}H, ^{13}C, and ^{31}P NMR, mass and CHN elemental analysis spectral data and are described in the experimental section. In the IR spectra, the absorption bands in the regions of 1155–1298 cm^{-1} correspond to P = O stretching frequency. In the ^{1}H NMR spectra, the chemical shift values in the region δ 1.56–1.58 ppm were assigned to $-CH_3$, 3.52–4.01 ppm was assigned to $-OCH_2$ protons, 3.80–4.01 ppm was assigned to –CH protons of isopropyl group ($-CH-(CH_3)_2$. Further, the structures of the titled compounds **3(a–e)** and **6(a–e)** were confirmed by the corresponding ^{13}C, ^{31}P NMR chemical shift values, molecular ions, and fragmentation ion peaks in mass spectra.

ANTIMICROBIAL ACTIVITY

Antibacterial Activity

The newly synthesized dialkyl heteroaryl phosphonates **3(a–e)** and **6(a–e)** were tested for their antibacterial activity against two Gram +Ve bacterial strains, *Staphylococcus aureus*, *Pseudomonas aeruginosa*; two Gram –Ve bacterial strains, *Klebsiella pneumoniae*

Table 1 Solvent effect on the synthesis of dialkyl heteroaryl phosphonates **3(a–e)** and **6(a–e)** in the presence of 37% $BF_3.SiO_2$ and 37% nano-$BF_3.SiO_2$

Entry	Catalyst (g)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	37% $BF_3.SiO_2$ (0.3)	Methanol	Reflux	8.0	30
2	37% $BF_3.SiO_2$ (0.3)	DCM	45	6.0	68
3	37% $BF_3.SiO_2$ (0.3)	Toluene	Reflux	7.5	62
4	37% $BF_3.SiO_2$ (0.3)	DMF	Reflux	6.5	50
5	37% $BF_3.SiO_2$ (0.3)	ACN	Reflux	7.0	68
6	37% $BF_3.SiO_2$ (0.3)	1,4-dioxane	Reflux	6.0	45
7	37% $BF_3.SiO_2$ (0.3)	Solvent-free	50	5.0	80
8	37% Nano-$BF_3.SiO_2$ (0.3)	Methanol	Reflux	6.0	78
9	37% Nano-$BF_3.SiO_2$ (0.3)	DCM	45	5.0	74
10	37% Nano-$BF_3.SiO_2$ (0.3)	Toluene	Reflux	6.5	70
11	37% Nano-$BF_3.SiO_2$ (0.3)	DMF	Reflux	6.0	68
12	37% Nano-$BF_3.SiO_2$ (0.3)	ACN	Reflux	6.0	64
13	37% Nano-$BF_3.SiO_2$ (0.3)	1,4-Dioxane	Reflux	5.5	68
14	37% Nano-$BF_3.SiO_2$ (0.3) (first run)	Solvent-free	50	3	88
15	37% Nano-$BF_3.SiO_2$ (0.3) (second run)	Solvent-free	50	3	87
16	37% Nano-$BF_3.SiO_2$ (0.3) (third run)	Solvent-free	50	3	85
17	37% Nano-$BF_3.SiO_2$ (0.3) (fourth run)	Solvent-free	50	3	78
18	37% Nano-$BF_3.SiO_2$ (0.3) (fifth run)	Solvent-free	50	3	65

and *Bacillus megaterium*; two Gram –Ve antibiotic resistant bacterial strains, mutant Escherichia *coli* (Streptomycin resistant) and donor *E. coli* (Rifampicin resistant) bacteria, by the agar well diffusion method using Amoxiclav (SD063, Himedia) as a standard drug. The diameter of inhibition zones in millimeters (DIZ) are represented in Table S1 (Supplemental Materials) and the minimum inhibitory concentrations (MIC) of the synthesized compounds are presented in Table S2 (Supplemental Materials).

Compounds **3a, 3b, 3c,** and **3e** have shown potent antibacterial activity against all the tested pathogens whereas compound **3d** has shown potent antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Compound **6a** showed potent antibacterial activity against *Pseudomonas aeruginosa and Klebsiella pneumoniae*. Compound **6b** has shown potent antibacterial activity against *Staphylococcus aureus and Klebsiella pneumoniae*. Compound **6d** showed potent antibacterial activity against *Pseudomonas aeruginosa.*

Antifungal Activity

The fungal strains *Aspergillus niger* and *Penicillium spinulosum* were used for testing the antifungal activity of the newly synthesized compounds **3(a–e)** by employing the poison plate technique. Fluconazole (SD 114, Himedia) was used as a standard drug. The results of the tested samples show that all the newly synthesized compounds exhibited potent to good activity against the tested micro organisms as represented in Table S3.

Compounds **3a** and **3e** showed potent antifungal activity against both the tested pathogens whereas compounds **3b** and **3d** showed potent antifungal activity against *Aspergillus niger*. In addition, the newly synthesized compounds **3(a–e)** and **6(a–e)** also showed potent activity against antibiotic resistant bacteria. We concluded that the newly synthesized compounds **3(a–e)** and **6(a–e)** have multidrug resistant activity.

EXPERIMENTAL

All chemicals were purchased from Merck, Aldrich, and S. D. Fine-chem. (India) for use without further purification. Solvents were distilled from the appropriate drying agents and degassed before use. Melting points were determined in open capillaries on Guna melting point apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR 5300 using KBr discs. ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometer. Mass spectra were recorded on an API 3000 mass spectrometer (positive mode). The progress of the reactions was monitored by TLC on Merck silica plates. Results are presented as chemical shift δ in ppm, multiplicity, J values in Hertz (Hz), number of protons, and proton position. Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), and m (multiplet).

Synthesis of Dialkyl Heteroaryl Phosphonates 3(a–e) and 6(a–e)

To 3-bromoquinoline **(1)** (208.09 mg, 0.001 mol), triethylphosphite **(2b)** (166.16 mg. Nano-BF_3.SiO_2 (300 mg) was added and the reaction mixture was refluxed at 50 °C for 3–5 h. After the completion of the reaction (confirmed by TLC), the reaction mixture was dissolved in DCM (10 mL) and filtered to remove the catalyst. The filtrate was concentrated under vacuum and the resulting crude material was purified on short column of silica gel using ethyl acetate:*n*-hexane (3:1) to obtain the final product diethyl quinolin-3-ylphosphonate **(3b)**. The same experimental procedure was utilized for synthesizing the remaining title compounds. Complete characterization of the products and representative ^{1}H, ^{13}C, and ^{31}P NMR spectra and mass spectra for 3a and 6a (Figures S1–S8) are presented in the Supplemental Materials.

Diethyl Quinolin-3-ylphosphonate (3b)

Yield: 88%, mp: 201–203°C. IR (KBr, cm^{-1}): 1218 (P=O, str), 1095 (P-C, str); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.59 (t, J = 6.8 Hz, 6H, $H_{12,\ 14}$), 3.53–3.59 (q, 4H, $H_{13,\ 14}$), 8.90 (s, 1H, H_2), 8.66 (s, 1H, H_4), 7.62–7.75 (q, 1H, H_6), 7.76–780 (q, 1H, H_7), 7.99 (d, J = 8.4 Hz, 1H, H_5), 7.93 (d, J = 8.4 Hz, 1H, H_8); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 17.1 ($C_{12,\ 14}$), 79.0 ($C_{11,\ 13}$), 151.4 (C_{10}), 154.1 (C_2), 137.8 (C_4), 130.5 (C_7), 129.2 (C_8), 128.1 (C_9), 127.8 (C_5), 124.9 (C_6), 122.5 (C_3); ^{31}P NMR (DMSO-d_6, 161.9 MHz): δ 16.6. M/s (positive mode) (*m*/*z*): 266 ($M+H^+$). Anal. calcd. for $C_{13}H_{16}NO_3P$: C 58.87, H 6.08, N 5.28; found: C 58.85, H 6.12, N 5.26.

BIOLOGICAL ASSAY

Antibacterial Activity

Antibacterial activity of the newly synthesized dialkyl heteroaryl phosphonates **3(a–e)** and **6**(**a–e**) was assayed against two Gram +Ve bacterial strains, *S. aureus*, *P. aeruginosa*; two Gram –Ve bacterial strains, *K. pneumoniae* and *B. megaterium*; two Gram –Ve antibiotic resistant bacterial strains, mutant *E. coli* (Streptomycin resistant) and donor *E. coli* (Rifampicin resistant) bacteria, by the agar well diffusion method[25,26] using Amoxiclav (SD063, Himedia) as a standard drug. The results are presented in Table S1.

Determination of Minimum Inhibitory Concentration

The MIC represents the lowest concentration of the antimicrobial agent that prevents the development of visible growth after overnight incubation.[27] MIC measurements were performed using the modified agar well diffusion method. MICs of the test samples are represented in Table S2.

Antifungal Activity

Some of the compounds were tested for the antifungal activity against two fungal strains *A. niger, P. spinulosum* by the poison plate method[28] using Fluconazole (SD 114, Himedia) as a standard drug. The results are shown in Table S3.

CONCLUSION

In this study, we reported the synthesis of novel dialkyl heteroaryl phosphonates **3(a–e)** and **6**(**a–e**), in an efficient method using nano-BF_3.SiO_2 catalyst, with shorter reaction times, low temperatures and high yields under solvent-free conditions. Nano-BF_3.SiO_2 is an eco-friendly, easily available, less toxic, cost effective, reusable, and green solid catalyst. The newly synthesized dialkyl heteroaryl phosphonates **3(a–e)** and **6**(**a–e**) have shown potent to good activities against all the tested pathogens.

From this, we conclude that this method shows promise for the synthesis of biologically active phosphonate drugs or drug intermediates, and that compounds **3a**, **3b**, **3c**, and **3e** may prove useful as antimicrobial agents in future.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website at http://dx.doi.org/10.1080/10426507.2014.996643

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