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$LaCl_3.7H_2O$: An efficient catalyst for the synthesis of phosphinates (Michaelis–Arbuzov reaction) under neat conditions and their potential antimicrobial activity

MADHAVA GOLLA[a], RASHEED SYED[a], VENKATA RAMANA KATLA[a], SUBBA RAO DEVINENI[a], NARESH KONDAPALLI[b] and NAGA RAJU CHAMARTHI[a,*]

[a]Department of Chemistry, [b]Department of Biochemistry, Sri Venkateswara University, Tirupati 517 502, India
e-mail: rajuchamarthi10@gmail.com

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Abstract. An expeditious neat procedure was developed for the synthesis of a series of new methyl phenyl heterocyclic phosphinates (**3a–l**) through Michaelis–Arbuzov reaction by the reaction of various heterocyclic halides (Cl or Br) (**1a–l**) with dimethyl phenylphosphonite (**2**) under N_2 atmosphere using a heterogeneous catalyst, $LaCl_3.7H_2O$. The advantages of the developed procedure are good yields (80–89%) of the products, less reaction time (2–3 h), avoiding toxic catalysts and harmful solvents and easy work-up procedure. Further, antimicrobial activity of the synthesized compounds was evaluated at different concentrations 50, 100 and 150 μg/mL. Biological data revealed that compounds **3i**, **3j** and **3h**, **3j** exhibited potential antibacterial and antifungal activities, respectively, while the rest of the compounds showed moderate antimicrobial activity.

Keywords. Michaelis–Arbuzov reaction; neat reaction; $LaCl_3.7H_2O$ catalyst; antimicrobial activity.

1. Introduction

It is well-known that organophosphorus compounds bearing C–P bond, phosphonates/phosphinates have wide range of applications in the fields of industry, agriculture, medicine and synthetic chemistry as catalysts and synthetic intermediates.[1] Particularly, phosphinates are conveniently consist of C–P bond which is formed by the reaction of trivalent phosphorus nucleophile with an electrophilic carbon[2] have been found in many synthetic and biological applications. For example, diarylphosphinate moieties have been found in various practical and scientific uses such as manufacturing of flame retardants,[3] advanced polymers,[4] membranes,[5] therapeutics[6] and catalytic antibodies.[7,8] As well as, diaminophosphinates are powerful inhibitors of HIV-1 protease,[9] monoaryl hydrogen phosphinates are useful for an oxidation couplings,[10] and hydrophosphinylation of multiple bonds[11] and aryl-phosphoindole acts as non-nucleoside reverse transcriptase inhibitors.[12] Hence, researchers have focused their attention recently in the synthesis of C–P linked organophosphorus compounds.

Michaelis–Arbuzov reaction is very versatile and widely used synthetic method for the synthesis of phosphinates, phosphonates and phosphine oxides[13] by the reaction of alkyl/aryl halides with trialkylphosphite.[14] In the progress of the Michaelis–Arbuzov reaction, chemists have been confronted some deficiencies like elevated temperature required for the activation of the reaction and prolonged heating which led to the decomposition of the starting substrate resulting in limits to the application of such reactions to sensitive substrates. The reaction generates one equivalent of alkyl halide which can react with phosphite under reaction conditions to reduce the product and reaction efficiency. Removal of the trialkyl phosphites used in a large excess and weaker electrophiles aryl/heteroaryl halides or vinyl halides giving lower yields are additional problems.

Catalytic methods play a special role in synthetic organic chemistry for progress of the reactions in simple fashion. Therefore, researchers have developed various stress-free methods for C–P bond formation. A small number of reports were found in the literature on the formation of C–P bond in the presence of Lewis acid catalysts such as $BF_3.Et_2O$,[15] CuI,[16] $PdCl_2$[17] and $NiCl_2$[18] via Michaelis–Arbuzov reaction. However, these methods have some limitations in terms of reaction time, temperature, reaction work-up and yields of the products. $BF_3.Et_2O$ catalysed Arbuzov reaction took longer reaction time, copper-mediated reaction is very rare[16], and aryl and vinyl halides are involved in

*For correspondence

Arbuzov reaction at high temperature in the presence of $PdCl_2$ and $NiCl_2$.[19,20]

In recent years, the usage of lanthanum (III) chloride as a catalyst has attracted the considerable attention due to its reusability, low cost, easy handling and hence, a wide variety of reactions are effectively catalysed with simple work-up procedures.[21–23] Therefore, we developed a neat procedure for the synthesis of new heterocyclic phosphinates by reacting various heterocyclic halides with dimethyl phenylphosphonite through Michaelis-Arbuzov reaction in the presence of an inexpensive heterogeneous catalyst, $LaCl_3.7H_2O$ under solvent-free conditions.

2. Experimental

All chemicals were purchased from Sigma-Aldrich and Merck, and used without further purification. Solvents used for spectroscopic and other physical studies were reagent grade and were further purified by literature methods.[24] Glassware was dried in oven at 150°C prior to use and all the reactions were conducted under nitrogen atmosphere. Melting points were examined in an open capillary using GUNA digital melting point apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR spectrophotometer using KBr pellets. ^1H,^{13}C and ^{31}P NMR spectra were recorded on a Bruker 400 MHz spectrometer operating at 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR and 161.9 MHz for ^{31}P NMR in DMSO-d_6 solvent. Tetramethylsilane in ^1H, ^{13}C NMR and 85% H_3PO_4 in ^{31}P NMR were used as internal and external standards, respectively. ESI mass spectra were recorded on a MLP 2103 mass spectrometer. Elemental analysis was performed on Thermo Finnigan FLASH EA 1112 instrument. Chemical shifts were recorded in parts per million (ppm) and multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet).

2.1 *General procedure for synthesis of the title compounds (**3a–l**)*

3-Bromoquinoline **(1a)** (0.20 mL, 0.001 mol), dimethyl phenylphosphonite (0.23 mL, 0.001 mol) and Lewis acid catalyst, $LaCl_3.7H_2O$ (20 mol%) were taken into a round bottom flask (50 mL) flushed with nitrogen. The reaction mixture was stirred for 2 h at 50°C under N_2 atmosphere. The progress of the reaction was checked by TLC using ethyl acetate: *n*-hexane (1:1) as an eluent. After completion of the reaction, the reaction mixture was dissolved in 10 mL of ethyl acetate and then filtered-off to remove the catalyst. The residue i.e., catalyst was further washed with ethyl acetate (3 × 5 mL) and the combined organic layer was concentrated under reduced pressure to obtain the crude product, methyl phenyl (quinolin-3-yl)phosphinate **(3a)**. The crude product was purified by column chromatography using ethyl acetate: hexane (1:3) as an eluent. The same procedure was employed to synthesize further title compounds **3(a–l)** (table 4).

2.1a *Methyl phenyl(quinolin-3-yl)phosphinate (**3a**)*: Brown solid, yield 72%, m.p 180–182°C. IR (KBr, υ_{max}, cm^{-1}): 1437 (P-C_{Ph}), 1385 (P-$C_{Heterocyclic}$), 1267 (P = O), 1043 (P-O-CH_3). ^1H NMR (DMSO-d_6): δ 8.61 (s, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 7.90–7.40 (m, 9H, Ar-H), 3.31 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 151.3, 150.8, 136.4, 134.0, 132.5, 130.5, 129.4, 128.9, 128.6, 128.2, 128.0, 127.5, 127.0, 43.5 (d, J = 11.0 Hz). ^{31}P NMR (DMSO-d_6): δ 20.1. LC-MS m/z (%): 284 $(M+H, 45)^+$, 270 $(M+H-14, 100)^+$. Anal. Calcd. for $C_{16}H_{14}NO_2P$: C, 67.84; H, 4.98; N, 4.94; Found: C, 67.79; H, 4.93; N, 4.90.

2.1b *Methyl isoquinolin-4-yl(phenyl)phosphinate (**3b**)*: Colourless solid, yield 70%, m.p 196–198°C. IR (KBr, υ_{max}, cm^{-1}): 1446 (P-C_{Ph}), 1404 (P-$C_{Heterocyclic}$), 1269 (P = O), 1037 (P-O-CH_3). ^1H NMR (DMSO-d_6): δ 9.53 (s, 1H, Ar-H), 8.68 (s, 1H, Ar-H), 8.29–7.87 (m, 9H, Ar-H), 3.29 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 155.3, 151.3, 143.7, 136.4, 131.5, 131.0, 130.7, 129.2, 128.6, 127.4, 125.7, 125.2, 39.9 (d, J = 12.0 Hz). ^{31}P NMR (DMSO-d_6): δ 19.2. LC-MS *m/z* (%): 284 $(M+H, 100)^+$. Anal. Calcd. for $C_{16}H_{14}NO_2P$: C, 67.84; H, 4.98; N, 4.94; Found: C, 67.72; H, 4.96; N, 4.81.

2.1c *Methyl phenyl(quinolin-2-yl)phosphinate (**3c**)*: Pale yellow solid, yield 67%, m.p 186–188°C. IR (KBr, υ_{max}, cm^{-1}): 1440 (P-C_{Ph}), 1395 (P-$C_{Heterocyclic}$), 1260 (P = O), 1045 (P-O-CH_3). ^1H NMR (DMSO-d_6): δ 8.40 (d, 1H, J = 7.6 Hz, Ar-H), 7.98–7.44 (m, 9H, Ar-H), 7.25 (d, 1H, J = 7.2 Hz, Ar-H), 3.28 (s, 3H,-OCH_3). ^{13}C NMR (DMSO-d_6): δ 156.2, 147.0, 136.0, 134.0, 132.1, 131.2, 130.6, 129.7, 128.7, 128.5, 128.0, 126.5, 122.0, 42.5 (d, J = 11.0 Hz). ^{31}P NMR (DMSO-d_6): δ 23.5; LC-MS*m/z* (%): 284 $(M+H, 18)^+$, 270 (M+H-14, $100)^+$. Anal. Calcd. for $C_{16}H_{14}NO_2P$: C, 67.84; H, 4.98; N, 4.94; Found: C, 67.77; H, 4.95; N, 4.88.

2.1d *Methyl 4-amino-6-chloropyrimidin-2-yl(phenyl) phosphinate (**3d**)*: Colourless solid, yield 65%, m.p 178–180°C. IR (KBr, υ_{max}, cm^{-1}): 1450 (P-C_{Ph}), 1390 (P-$C_{Heterocyclic}$), 1258 (P = O), 1050 (P-O-CH_3). ^1H NMR (DMSO-d_6): δ 7.80–7.35 (m, 5H, Ar-H), 6.65

(s, 1H, Ar-H), 6.30 (s, 2H, Ar-NH_2), 3.34 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 166.1, 164, 163.2, 133.9, 132.1, 130.5, 128.6, 106.5, 40.7 (d, J = 10.0 Hz). ^{31}P NMR (DMSO-d_6): δ 21.5. LC-MS *m/z* (%): 284 (M+H, 100)$^+$, 286 (M+H+2, 32)$^+$; Anal. Calcd. for $C_{11}H_{11}ClN_3O_2P$: C, 46.58; H, 3.91; N, 14.81; Found: C, 46.52; H, 3.88; N, 14.76.

2.1e *Methyl 2-amino-4-hydroxy-6-methylpyrimidin-5-yl(phenyl)phosphinate* ***(3e)***: Colourless solid, yield 65%, m.p 66–68°C. IR (KBr, υ_{max}, cm^{-1}): 1439 (P-C_{Ph}), 1400 (P-$C_{Heterocyclic}$), 1265 (P = O), 1030 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 11.10 (s, 1H, Ar-OH), 7.86–7.30 (m, 5H, Ar-H), 6.35 (s, 2H, Ar-NH_2), 3.38 (s, 3H, -OCH_3), 2.32 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d_6): δ 172.1, 167.4, 157.5, 134.0, 133.3, 130.5, 128.7, 113.4, 43.6 (d, J = 12.0 Hz), 21.8. ^{31}P NMR (DMSO-d_6): δ 24.2. LC-MS*m/z* (%): 280 (M+H, 100)$^+$. Anal. Calcd. for $C_{12}H_{14}N_3O_3P$: C, 51.62; H, 5.05; N, 15.05; Found: C, 51.56; H, 5.01; N, 15.00.

2.1f *Methyl 4,6-dimethoxy-1,3,5-triazin-2-yl(phenyl) phosphinate* ***(3f)***: Yellow solid, yield 68%, m.p 148–150°C. IR (KBr, υ_{max}, cm^{-1}): 1435 (P-C_{Ph}), 1395 (P-$C_{Heterocyclic}$), 1260 (P = O), 1035 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 7.83–7.45 (m, 5H, Ar-H), 3.75 (s, 6H, Ar-OCH_3), 3.32 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 175.0, 168.2, 134.0, 132.1, 130.3, 128.5, 53.2, 46.8 (d, J = 11.0 Hz). ^{31}P NMR (DMSO-d_6): δ 22.5. LC-MS *m/z* (%): 296 (M+H, 15)$^+$, 282 (M+H-14, 100)$^+$. Anal. Calcd. for $C_{12}H_{14}N_3O_4P$: C, 48.82; H, 4.78; N, 14.23; Found: C, 48.75; H, 4.75; N, 14.18.

2.1g *Methyl phenyl(pyrimidin-2-yl)phosphinate* ***(3g)***: Brown solid, yield 72%, m.p 168–170°C. IR (KBr, υ_{max}, cm^{-1}): 1430 (P-C_{Ph}), 1385 (P-$C_{Heterocyclic}$), 1268 (P = O), 1045 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 8.60 (d, 2H, J = 7.8 Hz, Ar-H), 7.75–7.35 (m, 6H, Ar-H), 3.29 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 164.2, 157.0, 133.8, 132.0, 130.6, 128.7, 123.6, 42.8 (d, J = 14.0 Hz). ^{31}P NMR (DMSO-d_6): δ 25.2. LC-MS*m/z* (%): 235 (M+H, 100)$^+$. Anal. Calcd. for $C_{11}H_{11}N_2O_2P$: C, 56.41; H, 4.73; N, 11.96; Found: C, 56.35; H, 4.70; N, 11.91.

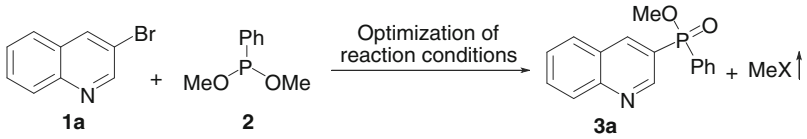
2.lh *Methyl 5-nitropyridin-2-yl(phenyl)phosphinate* ***(3h)***: Brown solid, yield 73%, m.p 140–142°C. IR (KBr, υ_{max}, cm^{-1}): 1446 (P-C_{Ph}), 1394 (P-$C_{Heterocyclic}$), 1264 (P = O), 1037 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 9.15 (s, 1H, Ar-H), 8.50 (d, 1H, J = 8.0 Hz, Ar-H), 7.85–7.40 (m, 6H, Ar-H), 3.36 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 162.0, 148.5, 146.1, 134.0, 132.4, 131.8, 130.7, 128.2, 126.0, 39.4 (d, J = 10.0 Hz). ^{31}P NMR (DMSO-d_6): δ 21.9. LC-MS *m/z* (%): 279 (M+H, 100)$^+$. Anal. Calcd. for $C_{12}H_{11}N_2O_4P$: C, 51.81; H, 3.99; N, 10.07; Found: C, 51.75; H, 3.96; N, 10.02.

2.1i *Methyl 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl(phenyl)phosphinate* ***(3i)***: Colour less solid, yield 65%, m.p 130–132°C. IR (KBr, υ_{max}, cm^{-1}): 1440 (P-C_{Ph}), 1387 (P-$C_{Heterocyclic}$), 1258 (P = O), 1065 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 11.05 (s, 2H, -NH), 7.90–7.50 (m, 6H, Ar-H), 3.37 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 163.5, 150.5, 141.8, 134.5, 132.6, 128.6, 128.4, 100.3, 43.5 (d, J = 12.0 Hz). ^{31}P NMR (DMSO-d_6): δ 19.5. LC-MS *m/z* (%): 267 (M+H, 100)$^+$. Anal. Calcd. for $C_{11}H_{11}N_2O_4P$: C, 49.63; H, 4.17; N, 10.52; Found: C, 49.55; H, 4.14; N, 10.47.

2.1j *Methyl phenyl(pyrazin-2-yl)phosphinate* ***(3j)***: Semi solid, yield 65%. IR (KBr, υ_{max}, cm^{-1}): 1439 (P-C_{Ph}), 1395 (P-$C_{Heterocyclic}$), 1262 (P = O), 1043 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 8.80 (d, 2H, J = 8.0 Hz, Ar-H), 8.56 (s, 1H, Ar-H), 7.87-7.34 (m, 5H, Ar-H), 3.32 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 151.2, 148.2, 145.8, 144.0, 134.1, 132.2, 130.6, 128.7, 41.6 (d, J = 13.0 Hz). ^{31}P NMR (DMSO-d_6): δ 23.5. LC-MS *m/z* (%): 235 (M+H, 100)$^+$; Anal. Calcd. for $C_{11}H_{11}N_2O_2P$: C, 56.41; H, 4.73; N, 11.96; Found: C, 56.36; H, 4.69; N, 11.91.

2.1k *Methyl 4,6-dimethoxypyrimidin-2-yl(phenyl) phosphinate* ***(3k)***: Semi solid, yield 68%, IR (KBr, υ_{max}, cm^{-1}): 1443 (P-C_{Ph}), 1379 (P-$C_{Heterocyclic}$), 1253 (P = O), 1035 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 7.78–7.37 (m, 5H, Ar-H), 6.54 (s, 1H, Ar-H), 3.68 (s, 6H, Ar-OCH_3), 3.36 (s, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6): δ 170.5, 159.8, 133.9, 132.1, 130.4, 128.2, 87.4, 52.3, 42.8 (d, J = 14.0 Hz). ^{31}P NMR (DMSO-d_6): δ 19.0 ppm; LC-MS *m/z* (%): 295 (M+H, 100)$^+$. Anal. Calcd. for $C_{13}H_{15}N_2O_4P$: C, 53.06; H, 5.14; N, 9.52; Found: C, 53.02; H, 5.11; N, 9.48.

2.1l *Methyl benzo[d]thiazol-2-yl(phenyl)phosphinate* ***(3l)***: Colourless solid, yield 70%, m.p 188–190°C. IR (KBr, υ_{max}, cm^{-1}): 1445 (P-C_{Ph}), 1400 (P-$C_{Heterocyclic}$), 1258 (P = O), 1055 (P-O-CH_3). ^{1}H NMR (DMSO-d_6): δ 8.25 (d, 1H, J = 7.8 Hz, Ar-H), 8.10 (d, 1H, J = 7.4 Hz, Ar-H), 7.78–7.35 (m, 7H, Ar-H), 3.35 (m, 3H, -OCH_3). ^{13}C NMR (DMSO-d_6), 155.8, 153.3, 135.0, 133.7, 132.0, 130.9, 128.5, 125.2, 124.6, 121.6, 121.2, 44.6 (d, J = 12.0 Hz). ^{31}P NMR (DMSO-d_6): δ 19.8. LC-MS *m/z* (%): 290 (M+H, 30)$^+$, 172 (M+H-



Scheme 1. Model reaction for the optimization of Michaelis–Arbuzov reaction.

118 100)$^+$. Anal. Calcd. for $C_{14}H_{12}NO_2PS$: C, 58.13; H, 4.18; N, 4.84; Found: C, 58.08; H, 4.15; N, 4.80.

2.2 *Reusability of the catalyst, $LaCl_3.7H_2O$*

The heterogeneous catalyst, $LaCl_3.7H_2O$ was filtered-off after the reaction was completed as residue. The isolated catalyst was washed three to four times with ethyl acetate to remove the tars on the catalyst and then dried under vacuum at 60°C for 10 h. The dried catalyst was reused for monitoring the reaction up to 5 cycles.

2.3 *Biological activity*

2.3a *Antibacterial screening test*: All the synthesized compounds **3(a–l)** were screened for their antibacterial activity against two Gram-positive strains, *Staphylococcus aureus* (ATCC-19433), and *Bacillus cereus* (ATCC-11778) and two Gram-negative strains such as *Escherichia coli* (ATCC-25922), and *Proteus vulgaris* (ATCC-29213) using filter paper disc diffusion method.[25] Different concentrations (50, 100 and 150 μg/mL) of test compounds and the standard, Ciprofloxacin were prepared in dimethylformamide (DMF) and DMF was used as negative control. The selected 24 h old bacteria cultured with 0.5 mL containing 1×10^7CFU/mL in nutrient broth were spread on nutrient broth-agar in Petri dishes. The paper discs (6 mm diameter, Whatman No. 2) were dried and dipped in known concentration of the prepared test samples. Then, these discs were placed on the culture and incubating for 24 h at 37°C. The clear zones of inhibition around the disc were measured (in mm). The experiments were performed in triplicate and the average value was taken as final result. Also, the percentage activity index for the compound was calculated using the following formula.

$$\%\text{Activity Index} = \frac{\text{Zone of inhibition by test compound(diameter)}}{\text{Zone of inhibition by standard(diameter)}} \times 100.$$

2.3b *Antifungal screening test*: The antifungal screening of the synthesized compounds **3(a–l)** was evaluated against three pathogenic fungal strains such as *Aspergillus niger* (MTCC-1881), *Fusarium oxysporum* (MTCC-1755) and *Aspergillus foetidus* (NCIM-505) using poison food technique with some modifications.[26] Ketoconazole was used as a standard for comparison of the activity. Potato dextrose agar (PDA) was used as basal medium for the test of fungal activity. Glass petri dishes were sterilized and 15 mL of sterilized melted (~45°C) was poured into each petri dish (90 mm). After solidification of the medium small portions of mycelium of each fungus were spread carefully over the centre of each PDA plate with the help of sterilized needles. The PDA plates were then incubated at 25 ± 2°C for three days. The prepared discs of the test samples were placed gently on the solidified agar plates freshly seeded with the test organisms with sterile forceps. Control discs were also placed on the test plates to compare the effect of solvent. The plates were

Table 1. Optimization of the catalyst and solvent effects for the synthesis of compound **3a**.

Entry	Catalysts	Solvent	Time (h)	Yield (%)
1	No catalyst	THF	16.0	Trace
2	$CuCl_2$ (15 mol%)	THF	6.0	48.5
3	$FeCl_3$(15 mol%)	THF	4.5	56.0
4	$AlCl_3$(15 mol%)	THF	4.5	59.5
5	$MgCl_2$(15 mol%)	THF	5.0	53.5
6	$CeCl_3.7H_2O$ (15 mol%)	THF	3.5	64.0
7	$LaCl_3.7H_2O$ (15 mol%)	THF	2.5	67.0
8	$LaCl_3.7H_2O$ (15 mol%)	Toluene	3.5	62.5
9	$LaCl_3.7H_2O$ (15 mol%)	CH_2Cl_2	4.0	57.0
10	$LaCl_3.7H_2O$ (15 mol%)	CH_3CN	4.0	60.0
11	$LaCl_3.7H_2O$ (15 mol%)	No solvent	2.5	72.5

Table 2. Examination of the catalyst amount and temparature effects for the synthesis of compound **3a**.

Entry	Catalyst loading	Temperature	Time (h)	Yield (%)
1	$LaCl_3.7H_2O$ (10 mol%)	50°C	3.5	66.0
2	$LaCl_3.7H_2O$ (15 mol%)	50°C	2.5	72.5
3	$LaCl_3.7H_2O$ (20 mol%)	50°C	2.5	78.0
4	$LaCl_3.7H_2O$ (25 mol%)	50°C	2.5	78.5
5	$LaCl_3.7H_2O$ (30 mol%)	50°C	2.5	78.5
6	$LaCl_3.7H_2O$ (20 mol%)	30°C	4.5	58.0
7	$LaCl_3.7H_2O$ (20 mol%)	40°C	3.0	68.0
8	$LaCl_3.7H_2O$ (20 mol%)	60°C	2.5	79.0
9	$LaCl_3.7H_2O$ (25 mol%)	50°C	2.5	79.0
10	$LaCl_3.7H_2O$ (30 mol%)	50°C	2.5	80.5

then kept in a refrigerator at 40°C for 24 h in order to have sufficient time for materials to a considerable area of the plates. After, the plates were incubated at 37°C for 72 h. The inhibition zones were measured and compared with the controls. The experiments were performed in triplicate and average value was taken as final result. The percentage activity index was calculated by the following equation.

$$\%\text{Activity Index} = \frac{\text{Zone of inhibition by test compound(diameter)}}{\text{Zone of inhibition by standard(diameter)}} \times 100.$$

3. Results and discussion

3.1 *Chemistry*

Various methods have been developed for the promotion of the Michaelis–Arbuzov reaction effectively. However, the developed procedures are associated with some drawbacks. In order to develop a suitable conditions for the formation of C–P bond through Michaelis–Arbuzov reaction, we have established new method in the part of our research programme using $LaCl_3.7H_2O$ catalyst under neat reaction conditions for the synthesis of new methyl phenyl heterocyclic phosphinates **3(a–l)**. The reaction conditions were optimized by taking 3-bromoquinoline **(1a)** and dimethyl phenylphosphonite **(2)** as models (scheme 1).

At first attempt, the model reaction was progressed without catalyst by preserving N_2 atmosphere result trace amount of the product, methyl phenyl (quinolin-3-yl) phosphinate **(3a)** (table 1 entry **1**) was observed after a long reaction time, 16 h even altering the reaction temperature 30–65°C. Further, to know the catalytic effect on this reaction, the model reaction was examined in THF using different catalysts, $CuCl_2$, $FeCl_3$, $AlCl_3$, $MgCl_2$, $CeCl_3.7H_2O$ and $LaCl_3.7H_2O$. The results suggested that the reaction was progressed from moderate to good in the presence of these Lewis acid catalysts (table 1 entry 2–7), although the high yield of the product (67.0%) was detected in $LaCl_3.7H_2O$ catalyst (table 1 entry 7). Hence, $LaCl_3.7H_2O$ catalyst was preferred to synthesize the title compounds. The previous study has revealed that the efficacy of the reaction also depends on solvent system. To our delight, the model reaction was run in different solvents, toluene, CH_2Cl_2, CH_3CN and solvent-free conditions (table 1 entry 8–11). It was found that the highest yield (72.5%) of the product **3a** obtained in neat reaction conditions as compared to other solvents (table 1 entry 11) in short reaction time. In addition, other factors like amount of the catalyst and the temperature are also influencing the reaction. Hence, the reaction has also been investigated by loading the catalyst, $LaCl_3.7H_2O$ in different amounts (10, 15, 20, 25, 30%) (table 2 entry 1–5) as well as the temperature effect was also examined at different temperatures (30, 40, 50, 60°C) (table 2 entry 5–10). The results showed that 20 mol% of the catalyst and 50°C are adequate to carry out the reaction efficiently (table 2 entry 3). The excess use of catalyst and adopting high temperature did not unveil significant changes in the improvement of the reaction.

The reusability of the catalyst, $LaCl_3.7H_2O$ was also examined up to five cycles after purifying the used

Table 3. Screening of reusability of the catalyst, $LaCl_3.7H_2O$ (20 mol%) for the synthesis of compound **3a**.

Entry	No. of runs	Time (h)	Yield (%)
1	1st	2.5	78.0
2	2nd	2.5	76.0
3	3rd	2.5	72.5
4	4th	2.5	66.0
5	5th	2.5	62.0

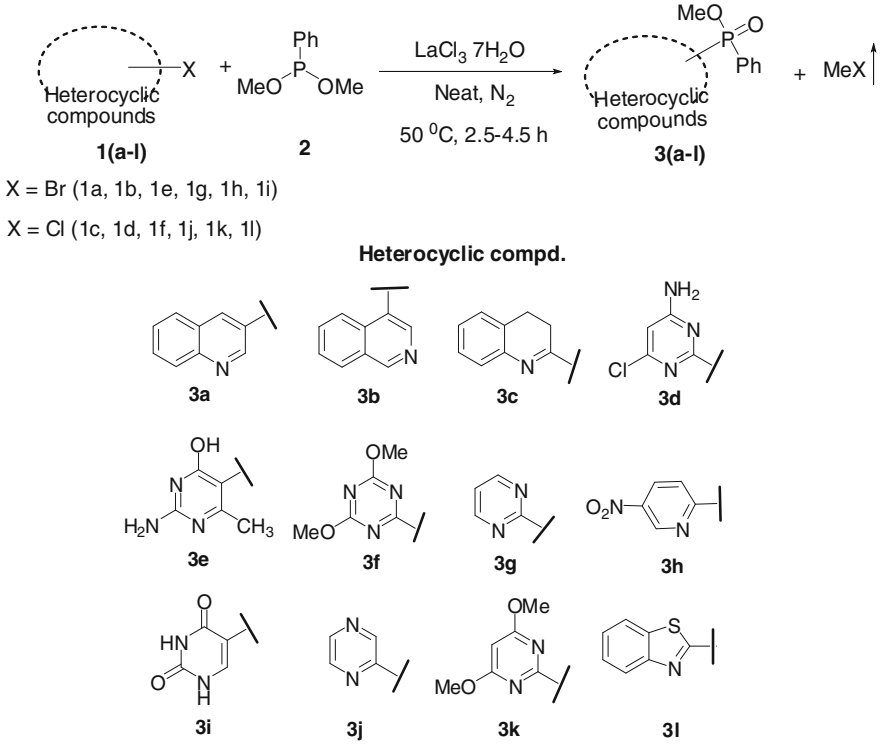
catalyst (table 3 entry 1–5). It was observed that until to three cycles the catalyst did not loose its significant catalytic activity.

After optimization of the reaction conditions, various title compounds were synthesized (scheme 2) by altering heterocyclic halides and the results are summarized in table 4. It was distinguished that brominated materials involved in the reaction meritoriously and offered good yields as compared with chlorinated material. Hopefully, we will continue further related research to improve the catalytic nature of the described catalyst by spreading on the solid support and application of it to synthesize various organic molecules in simple manner.

The chemical structures of all the title compounds **(3a–l)** were characterized by IR, NMR (^{1}H, ^{13}C, ^{31}P), mass spectral data and elemental analysis. IR spectra of the title compounds **(3a–l)** gave absorption bands in the regions of 1269–1253 cm^{-1}and 1055–1030 cm^{-1}confirmed the functionalities P = O and P–O–CH_3, respectively. In ^{1}H NMR spectra, aromatic protons of the title compounds **(3a–l)** gave chemical shift values in the region δ 8.29–7.34 ppm as complex multiplets and aliphatic –OCH_3 protons resonated as singlets in the region of δ 3.37–3.28 ppm. ^{13}C NMR spectral data of (**3a–l**) showed aromatic carbons in their corresponding region and P–O–CH_3 resonated as doublets in the region of δ 46.8–39.4 (d, J = 10.0–14.0 Hz). In ^{31}P NMR spectra, signals appeared as singlets in the region of δ 19.1–25.4 ppm corresponding to 'P' atom in all the title compounds.[27]

3.2 *Biological activity*

All the newly synthesized compounds were screened for their antibacterial activity against two Gram-positive bacterial strains such as *S. aureus* (ATCC-19433), and *B. cereus* (ATCC-11778) and two Gram-negative strains such as *E. coli* (ATCC-25922), and *P. vulgaris* (ATCC-29213) using filter paper disc diffusion method at different concentrations 50, 100 and 150 μg/mL and Ciprofloxacin was used as a standard. The bacterial zone of inhibition values of the title compounds **3(a–l)** in table S1 and the percentage of activity index in figures S1 and S2 (see supplementary information) are presented. The biological data revealed that compounds **3i, 3j** and **3h** against *S. aureus*, compound **3j** against *B. cereus,* compounds **3i** and **3h** against *E. coli* and compound **3j** against *P. vulgaris* showed promising activity. In overall antibacterial activity, the compounds **3i** and **3j** bearing uracil and pyrazine pharmacophoric groups, respectively, showed high antibacterial activity nearly to the standard drug, Ciprofloxacin than that of the remaining compounds.



Scheme 2. Neat and $LaCl_3.7H_2O$ catalysed synthesis for new methyl phenyl hetero/heteroarylphosphinates (**3a–l**).

A. niger (MTCC-1881), *F. oxysporum* (MTCC-1755) and *A. foetidus* (NCIM-505) fungal strains were used to screen the antifungal activity of the synthesized compounds **3(a–l)** fusing poison plate method at different concentrations 50, 100 and 150 μg/mL and Ketoconazole was used as a standard. The bio-screening data disclosed that compound **3j** showed potent activity and compounds **3h** and **3l** showed good activity against all the tested fungal strains which were closer to the standard drug, Ketoconazole. The fungal zone of inhibition values are given in table S2 and the results of percentage inhibition of the title compounds **3(a–l)** are given in

Table 4. Physical data for the synthesized title phosphinate derivatives **3(a–l)**.

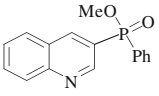
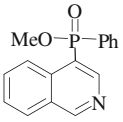
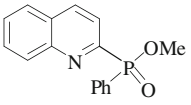
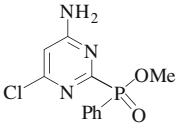
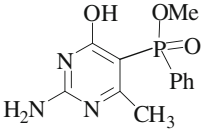
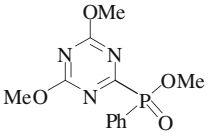
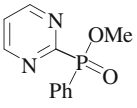
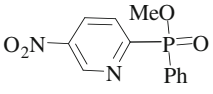
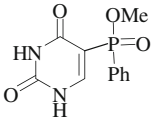
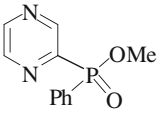
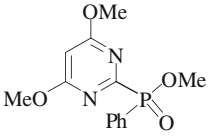
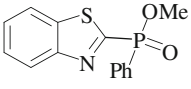
Compd.	Product	Time (h)	Yield (%)	m.p (°C)
3a		2.5	78.0	180–182
3b		2.5	74.5	196–198
3c		3.0	70.0	186–188
3d		3.5	71.5	178–180
3e		4.0	72.0	66–68
3f		3.5	72.0	148–150
3g		2.5	79.0	168–170
3h		3.0	81.5	140–142
3i		3.0	70.5	130–132
3j		4.5	73.0	–
3k		3.5	75.5	–
3l		3.5	71.5	188–190

figure S3 (see supplementary information). Overall, compound **3j** showed potent antibacterial and antifungal activities.

4. Conclusion

In summary, we conclude that $LaCl_3.7H_2O$ was found to be an efficient heterogeneous catalyst for the synthesis of new methyl phenyl heterocyclic phosphinates under neat reaction conditions through Michaelis–Arbuzov reaction. The method has several advantages: low cost, readily available, reusability of the catalyst, avoidance of toxic solvents, neat reaction conditions, easy work-up procedure, low reaction time, high yields of the products and significant generality. The *in vitro* antimicrobial activity of the newly synthesized compounds was evaluated against four bacterial strains and three fungal strains. Compound **3j** exhibited potent antibacterial as well as antifungal activities, nevertheless all the remaining compounds showed good to moderate activity. The present methodology could be useful in future for the synthesis of organic bio-active molecules/intermediates.

Supplementary information

The electronic supplementary information consists of antibacterial data (table S1, figures S1 and S2) and antifungal data (table S2 and figure S3) can be seen in www.ias.ac.in/chemsci.

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