Facile Synthesis of α-amino phosphonates derivatives in Room-Temperature Diisopropyl Ethyl Ammonium Sulphate [DIPEA][HSO_4]

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Abstract

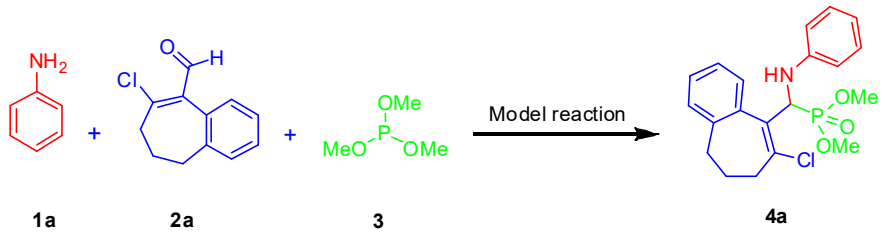
The diisopropyl ethyl ammonium Sulphate [DIPEA][HSO_4]-mediated cyclo-condensation pathway has been developed for the first time by a consecutive reaction of aniline, aldehydes and thioglycolic acid to afford α-amino phosphonates derivatives in excellent to promising yields at ambient temperature. The main advantage of this protocol are the ability to permit a wide range of functional groups, easy workup, short reaction times, high yields, solvent-free conditions and recyclability of the catalyst due to these application this protocol is environmentally benign.

Keywords: [DIPEA][HSO_4], Room-temperature, Ionic liquids, Environmentally benign, **α-**amino phosphonates derivatives

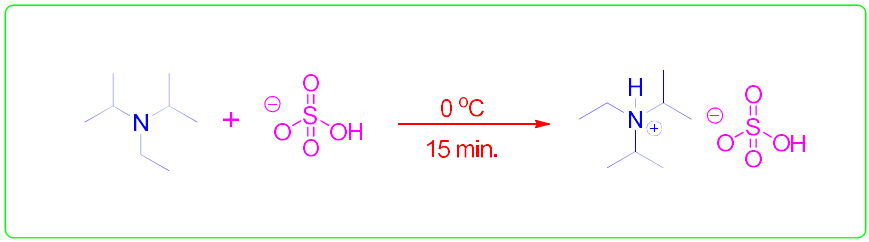
Introduction

Room-temperature ionic liquids (RTILs) have taken the great interest of the research community all over the world as a green alternative protocol to conventional ecofriendly media for synthesis, separation, catalysis and other various chemical tasks.[1-4] RTILs include diverse properties, such as nonvolatility, extensive liquid range, high thermal stability, low toxicity, excellent solubility, noncombustible and recyclability.[5] RTILs act as "neoteric solvents" for a broad range of chemical and industrial processes.

In this manuscript, we have developed [DIPEA][HSO_4] as ionic liquid mediated the proficient synthesis of α-amino phosphonates scaffolds under facile and benign protocol (**Schemes 1** and **2**).



Scheme 1. Synthesis of α-amino phosphonates derivatives **4a** by using [DIPEA][HSO_4] as RTIL



Scheme 2. Synthesis of Diisopropylethylammonium sulphate [DIPEA][HSO_4]

Multicomponent reactions (MCRs) are significant role in rapid and elegant synthesis of heterocyclic compounds from simple building blocks. MCRs are exhibit high atom-economy, simple experimental procedure and high selectivity protocol due to the construction of C-C and C-X (X= hetero atom) in one-pot.[8] MCRs in the drug discovery process offer a number of advantages over traditional approaches.[9] Furthermore, MCRs achieve the several advantages such as minimizes cost, time, effort and byproduct which are extremely agreeable with the goals of green and sustainable chemistry.[10]

There has been a continuous battle between human beings and disease causing microorganisms with a history of millennia. Infections caused by several microbes are posing a great threat to human survival.[11] Worsening the situation, the emergence of drug resistance is creating hurdles in the treatment.[12] In many immuno-compromised cases, it is not the

disease like AIDS or cancer itself but the secondary mycoses that cause death. Serious fungal infections are caused mostly by *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus* fumigates.[13] In addition to this, other *Candida* species such as *C. glabrata* and *C. krusei* are also emerging as serious hazards to patients. In the past two decades, the growth of fungal infections has increased by more than 200% and this is the third most common reason for bloodstream infections.[14] These health risks problems encourage the modifications and development of antifungal drugs by the design and synthesis of new chemical entities with high efficiency and broad spectrum activity.

The human body has a complex system of natural enzymatic and non-enzymatic antioxidant defenses which counteract the harmful effects of free radicals and other oxidants. Reactive oxygen species (ROS) are essential for an organism's essential activities, such as the regulation of cell proliferation, intracellular signaling and synthesis of biologically active compounds and energy. However, excessive production of ROS causes oxidative stress and chronic diseases such as cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, ageing, heart diseases and cancer. ROS are known to directly interact with all types of biomolecules, including proteins, lipids and DNA, resulting in oxidative cellular damage.[15] another important aspect regarding the antioxidant activity is the lipophilicity of the compounds. It is well established in the literature that the lipophilic compounds exhibit good antioxidant behavior in lipid systems.[16]

Phosphorous-containing compounds are attractive targets in the areas of medicinal and organic chemistry due to their wide range of pharmacological activities. Phosphonates possess more lipophilic nature and cell permeability along with physiological stability because the phosphorus-carbon bond is not susceptible to enzymatic degradation by phosphatases. α-aminophosphonate has become the center of interest based on their presence in a various biologically active compounds. They are phosphorous analogs of α-amino acids. α-aminophosphonic acid with oligopeptides group are excellent inhibitors of proteolytic

enzymes. 4-Thiazolidinones has been act as a fascination scaffolds (magical nucleus) and represents an significant group of heterocyclic compound with a extensive range of noteworthy biological activity such as antiviral,[17] cytotoxic,[18] anti-HIV,[19] anticancer,[20] herbicidal,[21] antibacterial[22] and antifungal.[23]

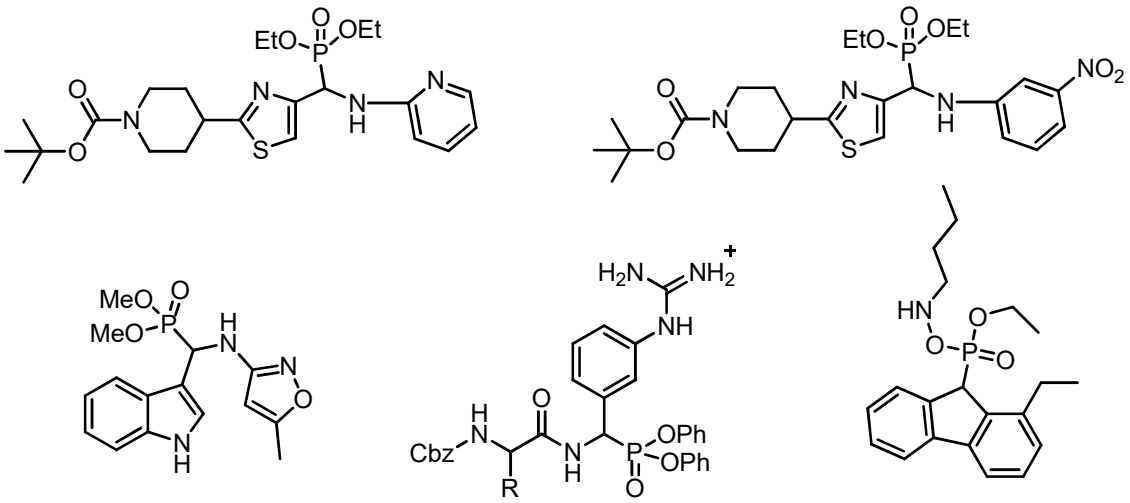


Fig. 1. Biological active compounds containing sulphonamide and oxazoles ring

A number of synthetic methods for the preparation of α-aminophosphonates have been carried out under various solvents using different types of catalysts like; $In(OTf)_3/MgSO_4$,[24a] GaI_3,[24b] $BiCl_3$,[24c] $Cu(OTf)_2$,[24d] $SbCl_3/Al_2O_3$,[24e] $InCl_3$[24f] and $ZrCl_4$[24g] are well documented. The synthesis of α-aminophosphonates have also been carried out in presence of ionic liquids,[25] Lewis acid-surfactant-combined catalyst[26] and even in absence of solvent and catalyst,[27] Lewis acids like $ZnCl_2$,[28a] $BF_3.Et_2O$,[28b] CdI_2/Benzene,[28c] and CdI_2/microwave.[28d] The synthesis of α-aminophosphonates have been carried out under solvent free conditions using trifluoroacetic acid (TFA),[29a] TsCl,[29b] $LiClO_4$,[29c] $Mg(ClO_4)_2$,[29d] metal triflate,[29e] $Na_2CaP_2O_7$[29f] and $ZrOCl_2.8H_2O$ or $ZrO(ClO_4)_2.6H_2O$.[29g] However, most of these procedures are sluggish, requires long reaction time, use of strong acidic condition, unsatisfactory yield, which also suffer from the formation of many side products.

According to the wide range of biological properties of *α*-aminophosphonates a large number of synthetic protocols have been developed for the synthesis of α-aminophosphonates. It is still necessary to develop a new simple, efficient, and general method, for this three-component reaction.

RESULTS AND DISCUSSION

Chemistry

In search of an efficient catalyst and the best experimental reaction conditions, the reaction of aniline **1,** aldehyde **2**, and trimethyl phosphite **3** at room temperature has been considered as a standard model reaction (**Scheme 1)**.

Initially when the reaction was carried out in absence of the catalyst, the product formed in trace amount (**Table 1**, entry 1). To determine the appropriate concentration of the catalyst [DIPEA][HSO_4], we investigated the model reaction at different concentrations of [DIPEA][HSO_4] such as 5, 10, 15, 20 and 25 mol%. The product formed in 70, 82, 89, 91 and 91% yields respectively (**Table 1**, entries 2-6). As increase in concentration of catalyst from 20 to 25 mol% does not increase the yield of product. This indicates that 20 mol% of [DIPEA][HSO_4] is sufficient for the reaction by considering yield of product.

Table 1. Effect of concentration of catalyst[a]

Entry	[DIPEA][HSO_4] mol %	Time (Min)	Yield[b] (%)

1	-	60	Trace
2	5	60	70
3	10	45	82
4	15	15	89
5	20	10	91
6	25	10	91

[a]**Reaction conditions**: Aldehyde (1.25 mmol), aniline (1.25 mmol), trimethyl phosphite (1.25 mmol), solvent-free at rt. [b]Isolated yield.

In the next step, we have compared the reported methods[19] using various ionic liquids for the synthesis of α-aminophosphonates (**Table 2**, entries, 1-7). In comparision with these, [DIPEA][HSO_4] provided better results in terms of high yield, solvent-free protocol and the reaction has been carried out at room temperature (**Table 2**, entry, 8).

Table 2. Comparision of ionic liquids used for the synthesis of α-aminophosphonate

Entry	Ionic liquid	Catalyst	Condition	Time	Yield (%)[a]	Reference
1	[bmim]PF_6	-	RT	8 hr	82	19a
2	[bmim]BF_4	-	RT	5 hr	90	19a
3	[bmim]OTf	$Yb(OTf)_3$	MW	2 min	55	19b
4	[bmim]SbF_6	$Yb(OTf)_3$	MW	2 min	72	19b
5	[bmim]PF_6	$Yb(OTf)_3$	MW	2 min	86	19b
6	[bmim]BF_4	$Yb(OTf)_3$	MW	2 min	99	19b
7	[bnmim][HSO_4] (50 mol %)	-	RT	1-3 hr	96	12d
8	[DIPEA][HSO_4]	-	RT	10 min	91	Present work

[a]Isolated yield.

To evaluate the effect of solvents, various solvents such as dichloromethane, tetrahydrofuran, 1,4-dioxane, toluene, acetonitrile and ethanol were used for the model reaction. It was observed that the use of solvents retards the rate of reaction and affords the desired product in lower yields than that for neat condition (**Table 3**, entries 1-6).

Table 3. Screening of solvents

Entry	Solvent	Yield[a] (%)
1	Dichloromethane	42
2	Tetrahydrofuran	45
3	1,4-Dioxane	48
4	Toluene	54
5	Acetonitrile	56
6	Ethanol	60
7	IL[b]	91

Reaction conditions: Aldehyde (1.25 mmol), aniline (1.25 mmol), trimethyl phosphite (1.25 mmol), [DIPEA][HSO_4] at rt for 20 min. [a]Isolated yield. [b]20 mol% [DIPEA][HSO_4]

The recyclability of the ionic liquid [DIPEA][HSO_4] was then studied and the results are shown in **Table 4**. After the completion of reaction, the reaction mixture was quenched with ice crystals and extracted with ethyl acetate. The residual ionic liquid was washed with diethyl ether, dried under vacuum at 60 ºC and reused for subsequent reactions. The recovered ionic liquid could be used for 5 times without obvious loss of catalytic activity of the ionic liquid (**Table 4**, entries 1-5).

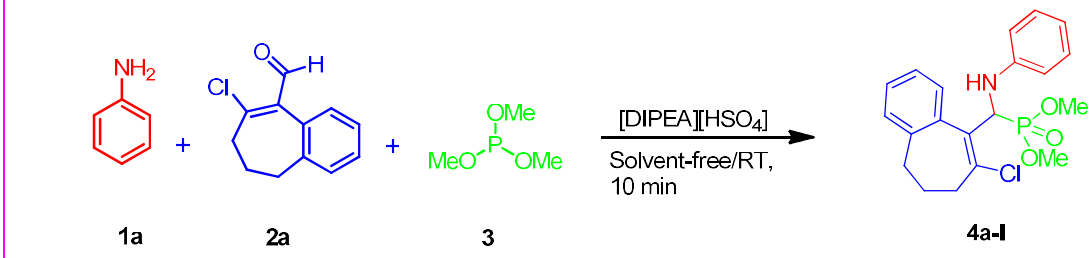
Table 4. Reusability of catalyst for model reaction

Entry	Run	Time[a] (Min)	Yield[b]

1	1	10	91
2	2	10	91
3	3	10	88
4	4	10	88
5	5	10	84

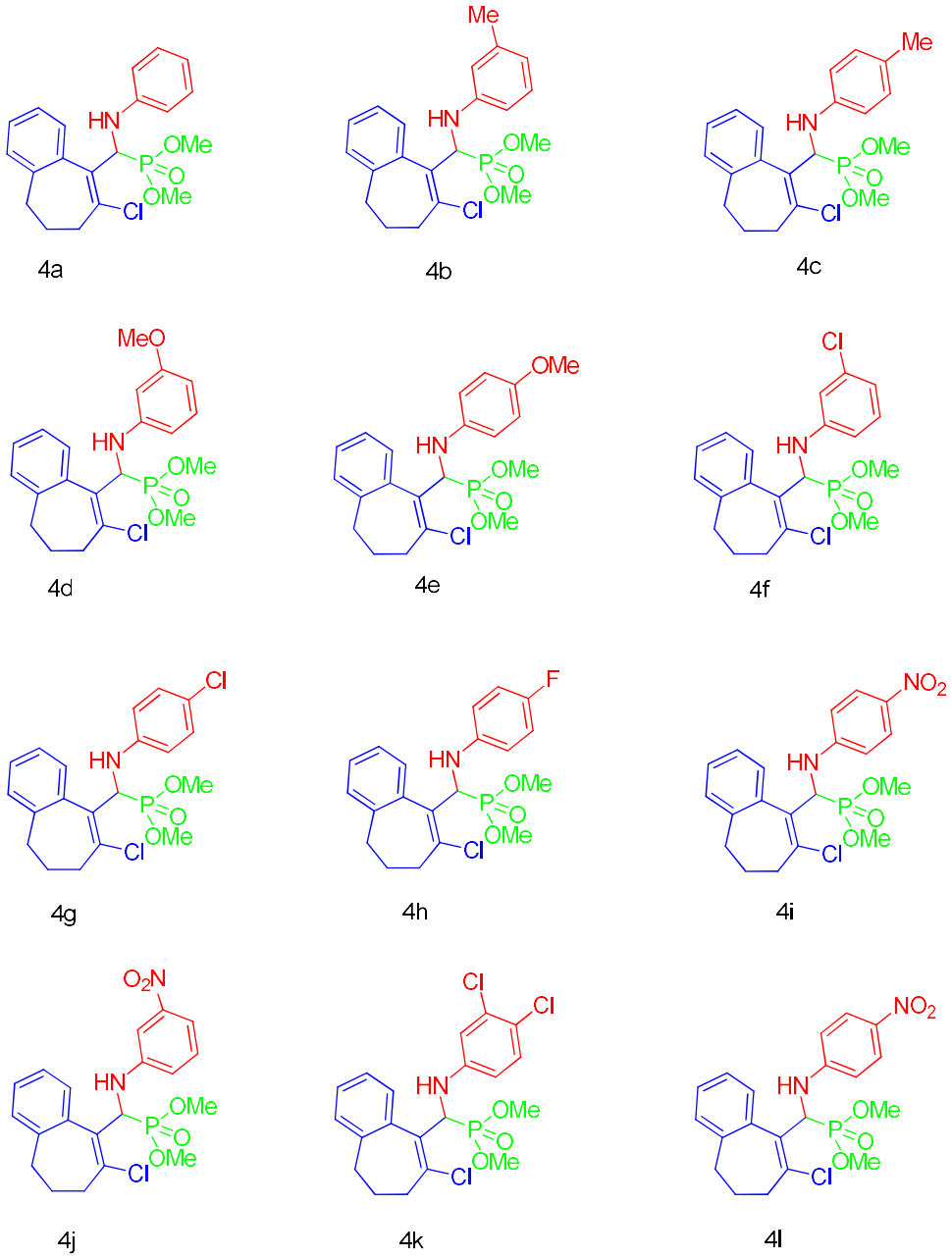
[a]Reaction progress monitered by TLC. [b]Isolated yield.

With these optimized reaction conditions for model reaction i.e. 20 mol% [DIPEA][HSO_4] catalyst, room temperature and solvent-free conditions, we have synthesized a series of α-aminophosphonates (**4a-n**) by reacting anilines (1**a-l**), aldehyde (**2a**), with electron donating and withdrawing groups) and trimethyl phosphite (**3**) in excellent yields (**Scheme 3**).



1a **2a** **3** **4a-l**

4a, R_1 = H, R_2 = H 4b, R_1 = Me, R_2 = H 4c, R_1 = H, R_2 = Me
4d, R_1 = OMe, R_2 = H 4e, R_1 =H, R_2 = OMe 4f, R_1 = Cl, R_2 = H
4g, R_1 = H, R_2 = Cl 4h, R_1 = Hl, R_2 = F 4i, R_1 = H, R_2 = NO_2
4j, R_1 = NO_2, R_2 = H 4k, R_1 = Cl, R_2 = Cl 4l, R_1 = H, R_2 = NMe_2

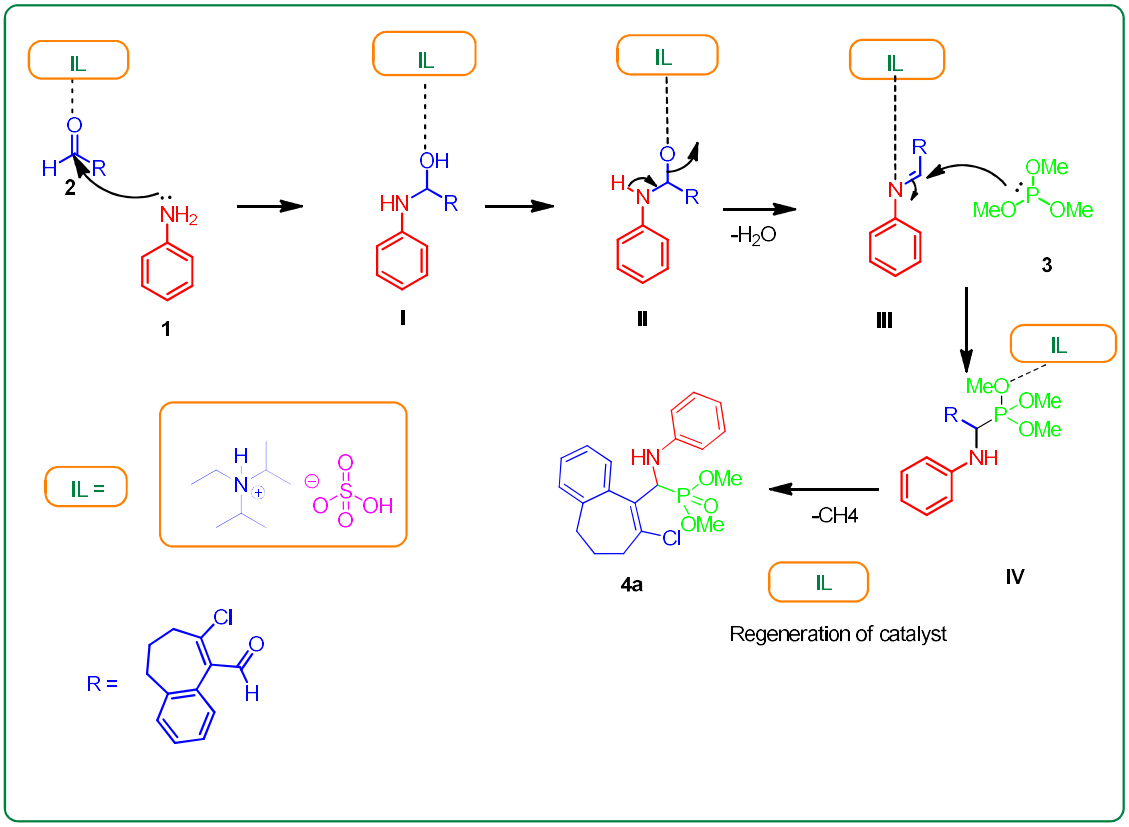


Scheme 3. Substrate scope for the synthesis of α-aminophosphonates derivatives using [DIPEA][HSO_4] catalyst.

Plausible Reaction Mechanism

Reaction mechanism cycle for the preparation of α-aminophosphonates analogues employing [DIPEA][HSO_4] is catalyst. In first step aldehyde activated by [DIPEA][HSO_4] followed by nucleophilic substitution of aniline results formation intermediate I. In next step removal of water molecules from intermediates **I** with the help of [DIPEA][HSO_4] to give imine product

II. In the third step intermediate **III** react with **3** afforded addition product **IV**. Further to form final product **4a** *via* removal of CH_4 molecule and regeneration of catalyst. Details reaction mechanism is presented in **Scheme 4.**



Scheme 4. Reaction mechanism cycle for the preparation of compounds **4a**.

Experimental section

Materials and methods

All chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC)

with a flame ionization detector (FID) with a capillary column (30 m 0.25 mm 0.25 lm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. Products were purified by column chromatography on 100–200 mesh silica gel. The 1H NMR spectra were recorded on 400 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded at 100 MHz and chemical shifts were reported in parts per million (d) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (J) values were reported in hertz (Hz). The splitting patterns of the proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) in 1H NMR spectroscopic analysis. The products were confirmed by ^{1}H and ^{13}C NMR spectroscopy analysis.

General Procedure for Synthesis of α-aminophosphonates derivatives (4a-l)

A mixture of aryl anilines (**1a-i**), aldehyde (**2a**) 1 mmol, trimethyl phosphite (**3a**) 1 mmol and ionic liquid 2 mmol **[DIPEA][HSO$_4$]** was stirred at rt for 10 min. The progress of the reaction was monitored by thin layer chromatography (*n*-Hexane/EtOAc 8:2). Further, addition of ice cold water (10 mL) was added to it and stirred for 10 min and filtered. The obtained solid was filtered, washed with cold water to remove the ionic liquid. The obtained crude compounds were recrystallized using ethanol. The synthesized compound is confirmed by MP, ^{1}H NMR and ^{13}C NMR spectra.

/4a/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)(phenylamino)methyl)phosphonate:

The cyclocondensation reaction of **1a, 2a** and **3** in ionic liquid for 40 min to give product **7a**. White solid; Mp: 210-212 °C; Yield: 91%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): ^{1}H NMR δ 7.31 (s, 1H), 7.21-7.07 (m, 5H), 6.69 (s, 1H), 6.66-6.54 (m, 2H), 4.56 (s, 1H), 3.76 (s, 1H), 3.60-3.37 (m, 6H), 2.30-2.26 (m, 2H), 2.16-2.12 (m, 2H) and 1.83-1.79 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 147.39, 143.11, 142.65, 138.05, 131.76, 129.16, 129.00

128.87, 126.41, 119.45, 115.65, 115.20, 97.30, 54.12-53.40, 37.50, 35.26, 34.98, 33.12 and 25.61.

***/4b/*dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)(m-tolylamino)methyl)phosphonate:**

The compound **4b** was obtained *via* cyclocondensation of **1b**, **2a** and **3** as white solid; Mp: 190-192 °C; Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.32 (s, 7H), 7.11 (dd, J = 23.4, 4.7 Hz, 28H), 6.53 (s, 4H), 6.52 (t, J = 1.4 Hz, 3H), 6.45 (d, J = 23.4 Hz, 17H), 4.82 (s, 7H), 3.92 (s, 7H), 3.59-3.37 (m, 43H), 2.67-2.63 (m, 14H), 2.36-2.29 (m, 35H) and 1.91-1.87 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 147.38, 142.53, 142.07, 139.94, 137.47, 131.19, 128.33, 128.22, 125.84, 121.24, 116.40, 113.13, 96.72, 53.55, 52.83, 36.92, 34.69, 34.41, 32.94, 25.04 and 20.64.

/4c/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)(p-tolylamino)methyl)phosphonate:

The compound **4c** was obtained *via* oxidative cyclocondensation of **1c**, **2a** and **3** as white solid; Mp: 194-196 °C ; Yield: 82%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.21-6.98 (m, 6H), 6.65-6.51 (m, 2H), 4.48 (s, 1H), 4.34 (s, 1H), 3.54-3.31 (m, 6H), 2.85-2.81 (m, 2H), 2.35-2.31 (m, 3H), 2.14-2.10 (m, 2H) and 1.85-1.81 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 144.32, 142.17, 141.71, 137.11, 130.82, 129.54, 129.33, 127.93, 126.75, 125.47, 115.07, 114.65, 96.36, 53.18, 52.46, 36.56, 34.32, 34.04, 32.57, 24.67 and 20.19.

/4d/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((3-methoxyphenyl)amino)methyl)phosphonate:

The compound **4d** was obtained *via* cyclocondensation of **1d**, **2a** and **3** as white solid; Mp: 176-178 °C; Yield: 82%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.29 (s, 1H), 7.17 (dd, J = 15.6, 15.0 Hz, 4H), 6.28 (d, J = 26.7 Hz, 2H), 6.18 (s, 1H), 4.70 (s, 1H), 4.41 (s, 1H), 3.81-

3.77 (m, 3H), 3.53-3.31 (m, 6H), 2.65-2.61 (m, 2H), 2.19-2.15 (m, 2H), 1.87-1.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 161.34, 149.15, 143.44, 142.98, 138.38, 132.09, 130.00, 129.21, 126.75, 108.19, 104.77, 101.36, 97.63, 56.37, 54.45, 53.74, 37.83, 35.60, 35.31, 33.85 and 25.94.

/4e/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((4-methoxyphenyl)amino)methyl)phosphonate:

The compound **4e** was obtained *via* cyclocondensation of **1e**, **2a** and **3** as white solid; Mp: 202-204 °C; Yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.35 (s, 1H), 7.23-7.14 (m, 3H), 6.85-6.71 (m, 2H), 6.69-6.55 (m, 2H), 5.14 (s, 1H), 3.94 (s, 1H), 3.83-3.79 (m, 3H), 3.51-3.29 (m, 6H), 2.83-2.79 (m, 2H), 2.16-2.12 (m, 2H) and 1.86-1.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 153.84, 144.05, 143.59, 140.93, 138.99, 132.70, 129.82, 127.36, 116.82, 116.42, 116.10, 115.65, 98.24, 56.98, 55.06, 54.35, 38.44, 36.21, 35.92, 34.46 and 26.55.

/4f/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((3-chlorophenyl)amino)methyl)phosphonate:

The compound **4f** was obtained *via* cyclocondensation of **1f**, **2b** and **3** as yellow solid; Mp: 186-188 °C; Yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.27 (s, 1H), 7.14 (dd, J = 19.4, 15.1 Hz, 4H), 6.70 (d, J = 15.7 Hz, 2H), 6.50 (s, 1H), 5.90 (s, 1H), 4.41 (s, 1H), 3.56-3.34 (m, 6H), 2.84-2.80 (m, 2H), 2.16-2.12 (m, 2H) and 1.86-1.81 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 148.19, 143.43, 142.97, 138.37, 133.60, 132.08, 129.81, 129.20, 126.74, 119.60, 115.97, 114.93, 97.62, 54.45, 53.73, 37.82, 35.59, 35.30, 33.84 and 25.93.

/4g/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((4-chlorophenyl)amino)methyl)phosphonate:

The compound **4g** was obtained *via* cyclocondensation of **1g**, **2c** and **3** as brown solid; Mp: 176-178 °C; Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.36 (s, 1H), 7.15 (dd, J = 5.2, 1.0 Hz, 4H), 7.10 (s, 1H), 6.51-6.37 (m, 2H), 4.55 (s, 1H), 4.09 (s, 1H), 3.57-3.35 (m, 6H), 2.64-2.60 (m, 2H), 2.38-2.34 (m, 2H), 1.96-1.92 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 148.49, 143.73, 143.27, 138.67, 133.89, 132.38, 130.10, 129.50, 127.04, 119.89, 116.27, 115.22, 97.92, 54.74, 54.03, 38.12, 35.89, 35.60, 34.14 and 26.23.

/4h/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((4-fluorophenyl)amino)methyl)phosphonate:

The compound **4h** was obtained *via* cyclocondensation of **1h**, **2c** and **3** as white solid; Mp: 190-192 °C; Yield: 81%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) δ 7.27 (s, 1H), 7.16 (t, J = 9.8 Hz, 3H), 6.94-6.88 (m, 2H), 6.61-6.57 (m, 2H), 5.74 (s, 1H), 4.41 (s, 1H), 3.57-3.34 (m, 6H), 2.85-2.81 (m, 2H), 2.16-2.12 (m, 2H) and 1.86-1.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 158.67, 146.37, 144.41, 143.95, 139.35, 133.07, 130.18, 127.72, 119.38, 118.07, 117.73, 117.49, 98.60, 55.43, 54.71, 38.80, 36.57, 36.29, 34.82 and 26.91.

/4i/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((4-nitrophenyl)amino)methyl)phosphonate:

The compound **4h** was obtained *via* cyclocondensation of **1i**, **2d** and **3** as white solid; Mp: 166-168 °C; Yield: 82%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 8.15-8.01 (m, 2H), 7.37 (s, 1H), 7.27-7.13 (m, 3H), 6.99-6.85 (m, 2H), 5.21 (s, 1H), 5.06 (s, 1H), 3.51-3.28 (m, 6H), 2.59-2.55 (m, 2H), 2.19-2.15 (m, 2H) and 1.87-1.83 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): δ 156.68, 144.41, 143.95, 139.36, 133.06, 130.18, 127.72, 127.04, 126.83, 117.61, 117.35, 98.60, 55.42, 54.71, 38.80, 36.57, 36.28, 34.82 and 26.91.

/4j/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((3-nitrophenyl)amino)methyl)phosphonate:

The compound **4j** was obtained *via* cyclocondensation of **7j**, **8g** and **9** as yellow solid; Mp: 168-170 °C; Yield:78%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.61 (s, 1H), 7.55 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 7.27-7.13 (m, 3H), 7.06 (s, 1H), 5.21 (s, 1H), 4.60 (s, 1H), 3.51-3.28 (m, 6H), 2.59- 2.55 (m, 2H), 2.19-2.15 (m, 2H), 1.86-1.82 (m, 2H).

/4k/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((3,4-dichlorophenyl)amino)methyl)phosphonate:

The compound **4k** was obtained *via* cyclocondensation of **7k**, **8c** and **9** as white solid; Mp: 172-174 °C; Yield: 83%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 7.28-7.03 (m, 5H), 6.57 (s, 1H), 6.41 (s, 1H), 5.83 (s, 1H), 4.39 (s, 1H), 3.57-3.35 (m, 6H), 2.64-2.60 (m, 2H), 2.17-2.13 (m, 2H) and 1.87-1.83 (m, 2H).

/4l/dimethyl ((8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)((4-nitrophenyl)amino)methyl)phosphonate:

The compound **4l** was obtained cyclocondensation of **7l**, **8c** and **9** as white solid; Mp: 178-180 °C; Yield: 83%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): δ 8.15-8.01 (m, 2H), 7.37 (s, 1H), 7.27-7.13 (m, 3H), 6.99-6.85 (m, 2H), 5.21 (s, 1H), 5.06 (s, 1H), 3.51-3.28 (m, 6H), 2.59- 2.55 (m, 2H), 2.19-2.15 (m, 2H) and 1.87-1.83 (m, 2H).

Biological activity

In vitro Antifungal and anti-oxidant evaluation

All the synthesized α-aminophosphonates was evaluated for their *in vitro* antifungal activity. The antifungal activity was screened against various fungal strains such as *Fusarium oxysporum* (NCIM 1332), *Aspergillus flavus* (NCIM 539), *C. albicans* (NCIM 3471), *C. neoformans* (NCIM 576) and *Aspergillus niger* (NCIM 1196) Minimum inhibitory concentration (MIC, µg/mL) values of all synthesized α-aminophosphonates were analyzed using standard agar dilution method as per CLSI guidelines.[31] All the experiments performed in triplicates and mean reading is taken as a final reading 5% DMSO was used as a negative control along with fluconazole and miconazole as the standard antifungal drugs (**Table 6**).

Table 5. *In vitro* antifungal and antioxidant activity of compounds **4a-l** MIC in (µg/mL).

Entry	R_1	R_2	Antifungal activity MIC (µg/mL)					DPPH IC_{50} (µg/mL)
			CA	***FO***	***AF***	***AN***	***CN***	
4a	H	H	100	100	50	50	200	22.11
4b	Me	H	150	125	100	100	125	18.24
4c	H	Me	100	100	125	100	150	19.14
4d	OMe	H	100	100	50	100	150	12.74
4e	H	OMe	50	50	50	50	75	15.76
4f	Cl	H	25	25	50	50	50	14.30
4g	H	Cl	25	25	25	25	25	12.90

4h	H	F	4.25	4.25	4.25	12.5	4.25	16.80
4i	H	NO_2	25	25	50	50	75	14.23
4j	NO_2	H	25	25	25	25	25	16.83
4k	Cl	Cl	7.25	7.25	7.25	12.5	7.25	24.20
4l	H	NMe_2	50	50	75	100	50	22.12
BHT	-	-	NT	NT	NT	NT	NT	16.47
AA								12.69
MA	-	-	25	25	25	25	25	NT
FA	-	-	6.25	6.25	6.25	12.5	6.25	NT

CA, Candida Albicans; FO, Fusarium Oxysporum; *AF*, *Aspergillus Flavus; AN, Aspergillus Niger* and *CN*, *Cryptococcus Neoformans.* BHT: Butylated hydroxy toluene; MA: Micanazole, FA: Fluconazole, NT: *Not tested, Note:* No activity was observed.*

The antifungal activity data suggest (**Table 5**), many of the synthesized α-aminophosphonates conjugates were exhibits promising antifungal activity. Some compounds were less active while some of them were found to be a wide range activity against all fungal strains. Compound **4f** (R_1 = Cl) with MIC values 25 µg/mL, exhibited equivalent activity compared to the standard drug miconazole against the fungicidal strain *C. albicans* and *Fusarium Oxysporum.* Compounds **4g** in which (R_2 = -Cl) showed excellent activity with MIC values 25 µg/mL against the strain *C. albicans, Fusarium Oxysporum*, *Aspergillus Flavus*, *Aspergillus Niger* and *Cryptococcus Neoformans* fungicidal strains. Compounds **7i** in which (R_2 = -Cl) exhibits superior activity against the *C. albicans and Fusarium Oxysporum*. Compounds **4h** in which (R_2 = -F) MIC values 4.25 µg/mL, exhibited prominent activity against the fungicidal strain such as *C. albicans, Fusarium Oxysporum*, *Aspergillus Flavus, Aspergillus Niger* and *Cryptococcus Neoformans*. The **4i** 4-thiazolidinone in which (R_3 = -NO_2) MIC values 25 µg/mL, exhibited equipotent activity against the fungicidal strain *C. albicans and Fusarium Oxysporum*, *respectively* compared to the standard drug Butylated hydroxy toluene. Compounds **4K** in which (R_1 and R_2= -Cl) showed excellent activity with

MIC values 7.25 µg/mL against the strain *C. albicans, Fusarium Oxysporum*, *Aspergillus Flavus*, *Aspergillus Niger* and *Cryptococcus Neoformans* fungicidal strains.

Antioxidant Activity:

The α-aminophosphonates hybrids were screened for their *in vitro* free radical scavenging activity against free radicals. All the synthesized compounds provide evidence that **4a-l** showed a concentration dependent anti-radical activity resulting from reduction of DPPH radicals to their non-radical forms and were measured using the 2,2 diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay.[32] Butylated hydroxytoluene (BHT) are used for standard drugs for the comparison of antioxidant activity and the all results are displays in **Table 5**.

According to the DPPH assay, compounds **4d**, **4e**, **4f**, **4g**, and **4i** exhibited better radical scavenging activity than the synthetic commercial antioxidant BHT, with IC_{50} values of 12.74, 15.76, 14.30, 12.90 and 14.23 µg/mL, respectively (**Table 5**). Similarly, compounds **4d** and **4g** shows excellent antioxidant activity compared to the standard antioxidant drug ascorbic acid with IC_{50} value 12.74 and 12.90 µg/mL respectively.

Antifungal activity

The α-aminophosphonates conjugates **4a-l** were screened for *in vitro* (**Table 5**) against the five human pathogenic fungal strains, as *Candida albicans* (NCIM 3471), *Aspergillus Flavus* (NCIM 539), *Fusarium oxysporum* (NCIM 1332), *Cryptococcus neoformons* (NCIM 576) and *Aspergillus niger* (NCIM 1196) as compared with standard reference drug fluconazole and miconazole. The minimum inhibitory concentration (MIC) values were determined using the standard agar method.

Conclusions

In conclusion, an environmentally efficient protocol has been established for the synthesis of functionalized α-aminophosphonates derivatives using an inexpensive and recoverable [DIPEA][HSO_4] catalytic solvent-free in 10 min. This, to the best of our knowledge, has no examples. Most of the synthesized compounds exhibit antifungal activity against *fungal* strain. Five compounds (**4f, 4g**, **4h**, **4i**, **4j** and **4k)** of the series displays exhibited promising activity against with MIC range 4.25-25 μg/mL, respectively. The antifungal activity results most of the synthesized α-aminophosphonates derivatives displays **4d**, **4e**, **4f**, **4g**, and **4i** promising radical activity. The synthesized α-aminophosphonates conjugates **4a-l** analyzed by ^{1}H NMR and ^{13}C NMR analysis methods.

Conflicts of interest

There are no conflicts to declare.

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References:

1. T. Welton, *Green Chem*. **13**, 225 (2011). **https://doi.org/10.1039/C0GC90047H**
2. C. Wang, L. Guo, H. Li, Y. Wang, J. Weng, L. Wu, *Green Chem*. **8**, 603 (2006). **https://doi.org/10.1039/B508325G**
3. C. Wang, W. Zhao, H. Li, L. Guo, *Green Chem*. **11**, 843 (2009). **https://doi.org/10.1039/B900042A**.
4. J. Weng, C. Wang, H. Li, Y. Wang, *Green Chem*. **8**, 96 (2006). **https://doi.org/10.1039/B508325G**
5. A. V. Dolzhenko, *Elsevier: Perth*, WA, Australia, **101** (2015).
6. T. Jiang, H. Gao, B. Han, G. Zhao, Y. Chang, W. Wu, L. Gao, G. Yang, *Tetrahedron Lett.* **45**, 2699 (2004). https://doi.org/10.1007/s10562-005-6503-9.
7. J. S. Wilkes, *Green Chem*. **4**, 73 (2002). **https://doi.org/10.1039/B110838G**
8. B. H. Rotstein, S. Zaretsky, V. Rai and A. K. Yudin, *Chem. Rev.,* **16**, 8323 (2014)**.** https://doi.org/10.1021/cr400615v.
9. A. Domling, W. Wang and K. Wang, *Chem. Rev.,* **6**, 3083 (2012). https://doi.org/10.1021/cr100233r.
10. R. A. Sheldon, *Pure Appl. Chem.* **7**, 1233 (2000). https://doi.org/10.1351/pac200072071233.
11. Kathiravan, M.K.; Salake, A.B.; Chothe, A.S.; Dudhe, P.B.; Wa tode, R.P.; Mukta, M.S.; Gadhwe, S. *Bioorg. Med. Chem*., **2012**, *20*(19), 5678-5698.
12. Payne, D.J.; Gwynn, M.N.; Holmes, D.J.; Pompliano, D.L. *Nat. Rev. Drug. Discov*., **2007**, *6*(1), 29-40.
13. (a) Vonberg, R.P.; Gastmeier, P. Nosocomial aspergillosis in out break settings. *J. Hosp. Infect*., **2006**, *63*(3), 246-254; (b) Marr, K.A. Oncol., Invasive Candida infections: the changing epidemiology. **2004**, *18*, 9-14
14. Lewis, R.E. *Curr. Med. Res. Opin*. **2009**, *25*, 1729-1762.

15. D. N. Pansare, N. A. Mulla, C. D. Pawar, V. R. Shende and D. B. Shinde, *Bioorg. Med. Chem. Lett.,* **24**, 3569 (2014). https://doi.org/10.1016/j.bmcl.2014.05.051.
16. M. L. Barreca, A. Chimirri, L. De Luca, A. M. Monforte, P. Monforte, A. Rao, M. Zappala, J. Balzarini, E. De Clercq, C. Pannecouque and M. Witvrouw, *Bioorg. Med. Chem. Lett.,* 13, 1793 (2001). https://doi.org/10.1016/S0960-894X(01)00304-3
17. H. Y. Li, R. Y.Chen, K. T. Ren, Phosphorus Sulfur Silicon, 1996, 119, 279.
18. G. V. Shitre, R. S. Bhosale, D. S. Karhale, S. Pombala, C. Ganeshkumar, K.V.S. Rama Krishna, S. V. Bhosale, Chemistry & Biology Interface, 2014, 4, 48.
19. A. Peyman, W. Stahl, K. Wagner, D. Ruppert, K. H. Budt, Bioorg. Med. Chem. Lett., 1994, 4, 2601.
20. J. Joossens, P. Van der Veken, A. M. Lambeir, K. Augustyns, and A. Haemers, J. Med. Chem. 2004, 47, 2411.
21. M. Sienczyk, J, Oleksyszyn, Tetrahedron Letters,2004, 45, 7251.
22. D. Bonarska, H. Kleszczynska, J, Sarapuk, Cell Mol Biol Lett., 2002, 7, 929.
23. M. V. Narayana Reddy, B. Siva Kumar, A. Balakrishna, C. S. Reddy, S. K. Nayak, and C. D. Reddy, ARKIVOC, 2007, 15, 246.
24. (a) Ghosh, R.; Maiti, S.; Chakraborty, A.; Maiti, D. *J. Mol. Cat. Chem.* **2004**, *53*, 210; (b) Sun, P. P.; Hu, Z. X.; Huang, Z. H. *Synth. Commun.* **2004**, *34*, 4293; (c) Zhan, Z. P.; Li, J. P. *Synth. Commun.* **2005**, *35*, 2501; (d) Paraskar, A. S.; Sudalai, A. *Arkivoc* **2006**, *(x)*, 183; (e) Ambica, K. S.; Taneja, S. C.; Hundal, M. S.; Kapoor, K. K. *Tetrahedron Lett.* **2008**, *49*, 2208; (f) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141; (g) Yadav, J. S.; Reddy, B. V. S.; Raj, S.; Reddy, K. B.; Prasad, A. R. *Synthesis* **2001**, 2277.
25. (a) Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P. *Green Chem.* **2002**, *4*, 436; (b) Lee, S.; Lee, J. K.; Song, C. E.; Kim, D. C. *Bull. Korean Chem. Soc.* **2002**, *23*, 667; (c) Zhou, Z.; Pei, Y.; Wu, L. *Org. Chem. Int.* **2012**. doi:10.1155/2012/375656; (d) Sadaphal, S. A.; Sonar, S. S.; Kategaonkar, A. H.; Shingare, M. S. *Bull. Korean Chem. Soc*. **2009**, *30*, 1054; (e) Lee, S.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, 1698.
26. Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669.

27. Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Saritha, B.; Prakash, S. J. *Synlett* **2003**, 505.

28. (a) Zou, J. *Pol. J. Chem.* **1981**, *55*, 643; (b) Laschat, S.; Kunz, H. *Synthesis* **1992**, 90; (c) Kabanchnik, M. M.; Ternovskaya, T. N.; Zobnina, E. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2002**, *38*, 480; (d) Kabanchnik, M. M.; Zobnina, E. V.;Beletskaya, I. P. *Russ. J. Org. Chem.* **2005**, *41*, 505.

29. (a) Akiyama, T.; Sanada, M.; Fuchibe, K. *Synlett* **2003**, 1463; (b) Kaboudin, B.; Jafari, E. *Synlett* **2008**, 1837; (c) Azizi, N.; Rajabi, F.; Saidi, M. R. *Tetrahedron Lett.* **2004**, *45*, 9233; (d) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263; (e) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692; (f) Elmakssoudi, A.; Zahouily, M.; Mezdar, A.; Rayadh, A.; Sebti, S. *Comptes Rendus Chim.* **2005**, *8*, 1954; (g) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 6029.