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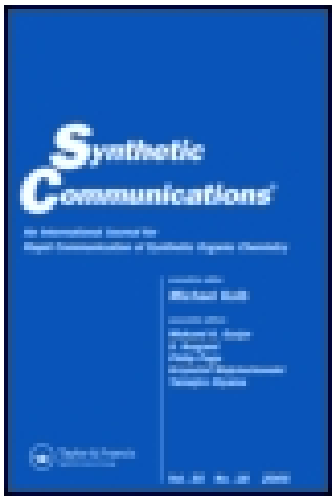

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Ionic Liquid-Promoted Phospha-Michael Reaction: Convenient Access to β-Nitrophosphonates

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Ionic Liquid–Promoted Phospha-Michael Reaction: Convenient Access to *β*-Nitrophosphonates

S. H. Jayaprakash[1], B. Satheesh Krishna[1], S. Santhi Sudha[1], N. Bakthavatchala Reddy[1], P. Sreelakshmi[1], K. Madhu Kumar Reddy[1], C. Suresh Reddy[1,]

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Abstract

A convenient and mild procedure is developed for β-nitrophosphonates via Phospha-Michael addition of phosphites to nitrostyrene at room temperature in the presence of 1,8-diazabicyclo- [5.4.0]undec-7-ene (DBU) based ionic liquid [DBUH][OAc]. The operational simplicity, convenient work-up, and reusability of the ionic liquid makes this method attractive.

KEYWORDS: Phospha-Michael addition, Ionic Liquid, [DBUH][OAc], C-P bond formation

INTRODUCTION

Chemistry of organophosphorus compounds continues to gain an increasing interest in the development of new methodologies for their preparation, owing to the biological, agricultural and organic synthesis.[1-4] Efforts to formulate more efficient procedures

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remain an important goal in organic synthesis. Construction of carbon-phosphorus (C-P) bond is one the most important synthetic step since they produce α- and β-functionalized phosphonic acid/ ester and their derivatives which serve valuable intermediates for the preparation of bioactive compounds.[5] Several C-P bond forming methodologies such as Michaelis-Arbuzov, Kabachnik-Fields, Pudovik reaction and Phospha-Michael reaction have been reported for the synthesis of different class of important organophosphorus compounds.[6–9]

Conjugate addition of phosphorus nucleophile (Michael donor) to activated olefins (Michael acceptor) is called Phospha-Michael reaction.[10,11] Among the various Michael acceptors, nitro alkenes are very attractive because the nitro group being the strong electron-withdrawing group induces generation of electrophilic center at its β-carbon.[12] The nucleophile facilitates addition of phosphorus at it forming C-P bond. Thus conjugate addition of phosphonates to nitroolefins is a convenient method for the synthesis of β-nitrophosphonates, which are precursors for the preparation of β-aminophosphonic acids.[13] In recent years, β-aminophosphonic acids received considerable attention due to their increasing applications in peptide and medicinal chemistry. They serve as the surrogates of β-amino acids in peptides and peptidomimetics with significantly improved bioactivities and pharmaco kinetic properties.[14,15] Though there are considerable number of reports on the development of new synthetic methodologies for β-nitrophosphonates,[16-19] the majority of these are suitable only for diaryl phosphite but not for dialkyl phosphites. Hence there is a necessity to develop an efficient and eco-friendly method applicable for both alkyl and aryl phosphites.

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Ionic liquids (**ILs**) have become the choice of organic green chemical synthesis, due to their distinctive properties, such as good thermal stability, negligible vapour pressure, ease of handling, potential for recycling, good solubilizing capability.[20-22] 1,8-Diazabicyclo[5.4.0]undec-7-ene acetate [(DBUH)(OAc)] being very useful as a non-nucleophilic task-specific organic ionic base[23-24] is successfully used as both reaction medium and catalyst for the synthesis of *β*-nitrophosphonates.

RESULTS AND DISCUSSION

Reaction of nitrostyrenes (**2a-h**) and phosphites (**1a-c**) at room temperature in the presence of [DBUH][OAc] ionic liquid (**3**) afforded *β*-nitrophosphonates (**4a-r**) in good yields (**Scheme 1**).

To establish the suitable reaction conditions, we have chosen the reaction between p-N, N-diethyl nitrostyrene, dimethyl phosphite as a model reaction (Table 1). It was carried by using various catalysts and catalyst free conditions at room temperature. The reaction did not progress with PPh_3, TBAc and catalyst free conditions (Table 1, Entries 4, 6 & 1). Lewis bases DMAP, DBU and TBAB produced low product yields (Table 1, Entries 2, 3 & 5). But DBU derived ILs (Table 1, Entries 11-13) offered good yields compared to other ionic liquids (Table 1, Entries 7-10). Although DBU derived ILs such as [DBUH][OAc], [DBUH][Lac] and [DBUH][Tfa] have the same cation $[DBUH]^+$, they showed the catalytic activities in the order: [DBUH][OAc] > [DBUH][Lac] > [DBUH][Tfa]. This suggests that the anions of the ILs show significant effect on the activities of the ILs for catalyzing this reaction. Even though [bmim][OAc] (Table 1,

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Entry 10) catalyzes this reaction, the reaction was sluggish and the product yields were low when compared to [DBUH][OAc] (Table 1, Entry 13). This implies that the cation part of the ILs exhibit considerable impact on the activities of the ILs for catalyzing this reaction. From the above results, it is deduced that both the cation and the anion of the IL plays important roles in catalyzing the reaction of phosphites with nitrostyrenes. So we have chosen [DBUH][OAc] as catalyst for the preparation of title compounds.

Further we studied the influence of catalyst concentration, temperature and reaction time for the model reaction. Increasing the catalyst concentration failed to improve the yield (Table 1, Entries 15, 16), while decreasing the catalyst concentration led to reduced yield (Table 1, Entries 14). The best results were obtained by performing the model reaction in the presence of 10 mol% of catalyst to yield the product in good yield. By elevating the temperature up to 70 °C, the yield remained unchanged (Table 1, Entries 17-19). Therefore, the optimum conditions for this reaction were: 10 mol% of catalyst at room temperature under solvent-free condition.

In order to establish the generality of this methodology, the synthesis of a variety of *β*-nitrophosphonates in the presence of [DBUH][OAc] ionic liquid under the optimized reaction conditions was investigated. The results of these studies are summarized in Table 2. The effect of the substituents on the phenyl ring of the nitrostyrenes was also investigated. Aliphatic nitrostyrene (**2h**) exhibited low reactivity towards phosphites and produced low product yield. Heterocyclic nitrostyrene (**2g**) and nitrostyrenes containing electron withdrawing groups (**2e & 2f**) showed moderate reactivity towards phosphites

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and produced moderate product yield. While simple phenyl nitrostyrenes (**2a**) and nitrostyrenes having electron donating groups (**2b, 2c & 2d**) exhibited good reactivity towards phosphite nucleophiles and consequently produced good product yields. The catalyst was compatible with functional groups such as Br, CN and -OMe. No competitive nucleophilic methyl ether cleavage was observed for the substrates which possessed -OMe group (Table 2, Entries 7-9), despite the strong nucleophilicity of phosphites.

From the experimental results it was noticed that diphenyl phosphite showed good nucleophilic character and produced good product yields, whereas diethyl and dimethyl phosphites displayed moderate nucleophilic character and gave moderate yields. The difference in the product yields may be explained on the basis of acidity of the phosphites. It was reported that pentavalent phosphorus remains in equilibrium with trivalent phosphorus which is attacking species at the carbon electrophilic center of the olefin, shown in Scheme 2.[25] This equilibrium is highly influenced by the acidity of the phosphite. Phosphite with increasing acidic character shifts the dynamic equilibrium towards the formation of trivalent state (**III**) as a result the rate of nucleophilic addition to the olefinic carbon reaction increases. For this reason diphenyl phosphite with pKa value 9.0 acts as a good nucleophile while dimethyl phosphite having pKa value 18.4 is not.

A plausible mechanistic route for this reaction is proposed in Scheme 3. Initially, nitrostyrene (**2a-h**) abstracts a proton from ionic liquid (**3**) to form the intermediates (**IV**) and (**V**).[26] Intermediate (**V**) subsequently undergoes a Michael-type addition with

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phosphite (**1a-c**) followed by proton shift provides the intermediate (**VII**) which loses a proton to the intermediate (**IV**) to regenerate the catalyst (**3**) and forms the desired *β*-nitrophosphonates (**4a-l**).

The reusability of the catalyst is an important factor from the economic and environmental point of view. Hence we investigated the possibility of reusability of the recycled catalyst [DBUH][OAc]. Catalytic activity of the recovered ionic liquid from the model reaction was checked in the subsequent runs (Figure 1). Our analysis and results reveal that ionic liquid can be reused multiple times even though there is much less loss in its activity.

In comparison with other catalysts employed for the model reaction, [DBUH][OAC] showed a much higher activity in terms of short reaction time and mild conditions (Table 3).

EXPERIMENTAL SECTION

General

Solvents and reagents were procured from Sigma-Aldrich & Merck and are used as such without further purification. Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus. IR spectra were recorded on FT-IR spectrometer. ^{1}H and ^{13}C spectra were recorded as solutions in $CDCl_3$ on a Bruker AMX 500 MHz spectrometer operating at 300 MHz for ^{1}H, 75.4 MHz for ^{13}C and 120 MHz for ^{31}P NMR. For ^{1}H and ^{13}C chemical shifts tetramethylsilane (TMS) was taken as

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an internal standard and 85 % H_3PO_4 was taken as an external standard for ^{31}P chemical shifts. ESI mass spectra were recorded on a Micromass Quattro LC instrument. Elemental analysis was performed on Thermo Finnegan Instrument.

General Procedure For Preparation Of Ionic Liquid [DBU][Ac]

[DBUH][OAc] ionic liquid was prepared according to the reported procedures.[23] In a 50 mL two necked round bottomed flask, one neck was blocked with nitrogen trap to maintain inert atmosphere and DBU (1 equiv.) was loaded through other neck. To this acetic acid (1 equiv.) was added drop wise over a period of 15 min with stirring. Throughout this addition the temperature was maintained between 0-5 °C. The resultant mixture was stirred overnight at 60 °C, after completion of the reaction a light yellow viscous oily liquid was obtained. Thus obtained oily residue was dried in vacuo at 60 °C for 12 h to afford [DBU][Ac] a light yellow viscous liquid.

Characterization data for [DBUH][OAc]: Light yellow viscous oily liquid, ^1H NMR (400 MHz, D_2O): δ 1.76 (s, 3H, CH_3), 1.52-1.67 (m, 6H), 1.84-1.90 (m, 2H), 2.39-2.65 (m, 2H), 3.16-3.19 (m, 2H), 3.28-3.44 (m, 4H); ^{13}C NMR (100 MHz, D_2O): δ 19.5, 23.3, 25.9, 27.3, 28.4, 32.8, 38.0, 48.2, 54.1, 165.9, 179.4.

General Procedure For The Synthesis Of B-Nitrophosphonates (4a-L)

In a typical experiment to synthesize β-nitrophosphonates (**4a-r**), nitrostyrene (**2a-h**, 1.0 mmol), phosphite (**1a-c**, 1.2 mmol) and the ionic liquid [DBUH][OAc] with the desired amount (10 mol %) were loaded into the reaction flask and stirred magnetically. After completion of the reaction, water was added to the reaction mixture and the

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products were extracted with ethyl acetate (3X15 mL). The combined ethyl acetate extract was dried over anhydrous Sodium sulphate (Na_2SO_4) and then concentrated through vacuum evaporation to obtain the crude product, which was further purified by column chromatography. The aqueous layer consists of [DBUH][OAc]. Water was evaporated under reduced pressure to recover the ionic liquid which was reused to perform the

Dimethyl (1-(4-(diethylamino)phenyl)-2-nitroethyl)phosphonate (4e): Yellowish liquid, Isolated yield = 88 %; IR: ν = 3026, 2893, 1641, 1581, 1324, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.10-6.60 (m, 4H, Ar), 4.89-4.85 (m, 2H, CH2), 3.96-3.89 (m, 1H, CH), 3.74-3.71 (d, *J*=10.8 Hz, 3H, OCH3), 3.54-3.52 (d, *J*=10.5 Hz, 3H, OCH3), 3.34-3.30 (q, *J*=7.01 Hz, 4H, 2CH2), 1.14 (t, *J*=7.09 Hz, 6H, 2CH3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 146.4, 127.4, 122.4, 112.9, 69.3, 56.4, 54.7, 48.2, 47.6, 38.7, 16.3, 15.8; ^{31}P NMR (120 MHz, $CDCl_3$): δ 22.73; MS (ESI): m/z 331 $[M+H]^+$; Anal. Calcd.for $C_{14}H_{23}N_2O_5P$: C, 50.91; H, 7.02; O, 24.22; Found: C, 50.73; H, 6.85; O, 24.11.

CONCLUSION

We have developed a neat and environmentally benign procedure for the construction of C-P bond. [DBU][AC] ionic liquid was used as an efficient catalyst for synthesis of β-Nitrophosphonates by the reaction of nitro olefins and dialkyl/aryl phosphites at room temperature under solvent-free conditions. The method is applicable for various Nitrostyrenes and afforded the corresponding β-Nitrophosphonates in moderate to good

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yields. The use of green, nontoxic, economical and reusable catalyst [DBUH][OAC] is the merit of this procedure.

CONFLICT OF INTEREST

We state that none of the authors have any conflict of interest in the context of this communication.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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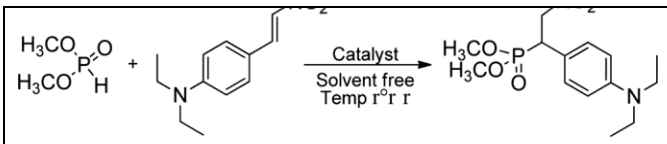
Table 1. Optimization of the model reaction under various conditions[a]



Entry	Catalyst (mol%)	Temp (°C)	Time (hrs)	Yield (%)[b]
1	No catalyst	rt	10.0	NR[c]
2	DMAP(10)	rt	8.0	33
3	DBU(10)	rt	8.0	52
4	PPh_3 (10)	rt	10.0	NR[c]
5	TBAB (10)	rt	8.0	26
6	TBAc(10)	rt	8.0	NR[c]
7	[bmim]HSO_4(10)	rt	6.0	41
8	[bmim][BF_4] (10)	rt	6.0	28
9	[bmim][Cl] (10)	rt	6.0	37
10	[bmim][OAc] (10)	rt	6.0	62
11	[DBU][Lac] (10)	rt	6.0	83
12	[DBU][Tfa] (10)	rt	6.0	78
13	[DBUH][OAc] (10)	rt	6.0	88
14	[DBUH][OAc] (5)	rt	9.0	79
15	[DBUH][OAc] (20)	rt	9.0	88
16	[DBUH][OAc] (30)	rt	9.0	88
17	[DBUH][OAc] (10)	50	9.0	88
18	[DBUH][OAc] (10)	60	12	88

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19	[DBUH][OAc] (10)	70	12	88

[a]Reactions conditions: N, N-diethyl-4-(2-nitrovinyl) aniline (1 mmol), dimethyl phosphite (1.2 mmol), solvent-free condition.

[b]Isolated yield

[c]No Reaction.

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Table 2. Scope for [DBUH][OAc] catalyzed synthesis of β-Nitrophosphonates[a]

Entry	2, Ar	1, R	4	Yield (%)[b]
1	2a, Ph	la, Ph	4a	89
2	2a, Ph	lb, Et	4b	83
3	2a, Ph	lc, Me	4c	81
4	2b, 4-$N(Et)_2C_6H_4$	lb, Et	4d	89
5	2b, 4-$N(Et)_2C_6H_4$	lc, Me	4e	88
6	2c, 4-MeC_6H_4	la, Ph	4f	91
7	2d, 4-$MeOC_6H_4$	la, Ph	4g	86
8	2d, 4-$MeOC_6H_4$	lb, Et	4h	83
9	2d, 4-$MeOC_6H_4$	lc, Me	4i	82
10	2e, 3-BrC_6H_4	la, Ph	4j	79
11	2e, 3-BrC_6H_4	lb, Et	4k	78
12	2e, 3-BrC_6H_4	lc, Me	41	76
13	2f, 4-CNC_6H_4	lb, Et	4m	78
14	2f, 4-CNC_6H_4	lc, Me	4n	77
15	2g, Thiophen-2-yl	lb, Et	4o	78
16	2g, Thiophen-2-yl	lc, Me	4p	75
17	2h, Me_2CH	lb, Et	4q	58
18	2h, Me_2CH	lc, Me	4r	51

[a]Reactions conditions:Nitro styrene (1 mmol), dimethyl phosphite (1.2 mmol), [DBUH][OAc] IL (10 mol %) at RT and solvent-free conditions.

[b]Isolated yield

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Table 3. Influence of different catalysts on the synthesis of Diphenyl (2-nitro-1-phenylethyl)phosphonate (**4a)**

Entry	Catalyst	Reaction conditions	Time (h/min)	Yield (%)[a]
1	TBD	THF/ rt	5min	90[17]
2	Quinidine thiourea/ 4Å MS	DCM/ 5 °C	0.5h	79[19]
3	Quinine	Xylene/ -55 °C	6days	82[16]
4	**[DBUH][OAC]**	**Neat/ rt**	**6.0h**	**89[b]**

[a]Isolated yield

[b]Present work

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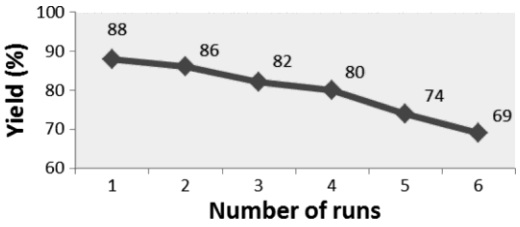
Figure 1. Recycling studies of [DBUH][OAc].



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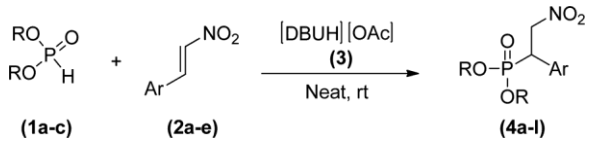
Scheme 1. Synthesis of β-nitrophosphonates (**4a-l**)



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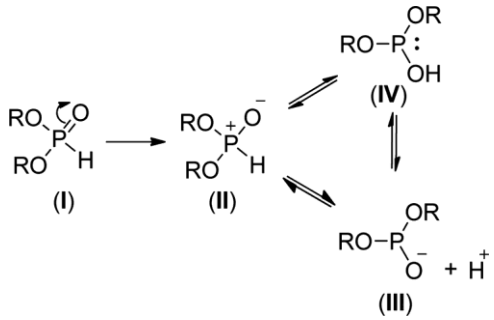
Scheme 2. Equilibrium between penta and trivalent phosphorus



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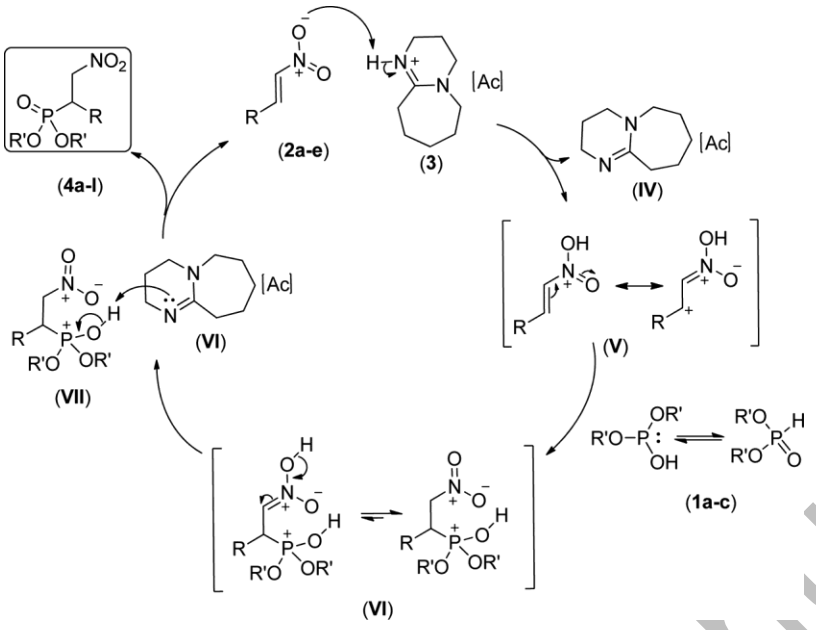
Scheme 3. Mechanism for the formation of β-nitrophosphonates



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