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Research Paper

Barium hydroxide catalyzed greener protocol for the highly efficient and rapid synthesis of α-hydroxyphosphonates under solvent free conditions

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Abstract: We present here a barium hydroxide catalyzed protocol for the cleaner, safer, and cost-effective hydrophosphonylation of aldehydes by a Pudovik reaction with diethyl phosphate under solvent free conditions. The corresponding diethyl 1-hydroxy arylmethylphosphonate derivatives obtained was with good to excellent yield (70- 98%).

Introduction

The toxicity, infallibility and volatile nature of many organic solvents are widely used in huge amounts for organic reactions have posed a serious intimidation to the environment [1].Thus, today's environmental concerns encourage the development of new environmentally benign synthetic processes by avoiding the use of corrosive reagents, harmful solvents and stoichiometric formation of inorganic waste [2, 3]. In the area of green chemistry solvent free reactions [4, 5] are gaining popularity, particularly in industry, because it may be both more environmentally benign and more economically beneficial. The solvent free approach of organic reaction opens up several possibilities for conducting selective functional group transformations more efficiently using variety of catalysts. The practical feasibility of solvent free protocol has been established and useful in many transformations[6-8]. These distinct advantages of solvent free reaction to eliminate the use of solvents thereby, preventing pollution at source in organic synthesis and easy recovery of the catalyst is today's need[9].

The synthesis of α-hydroxyphosphonates and α-hydroxyphosphonic acid has caught fascinating attention, particularly in connection with the search for biologically active surrogates for the corresponding carboxylic acids and phosphoric acids esters [10]. The α-hydroxyphosphonates were biological potent molecules due to interesting activities as pesticides, antibiotics, anticancers, antivirals, and enzyme inhibitors, including HIV proteas [11, 12], EPSP synthase [13], and thyrosin-specific

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Chemistry & Biology Interface, 2012, 2, 5, 314-321

protein kinas [14]. They are also valuable precursors for the construction of biologically significant α-functionalized amino-, keto- and acetoxy- phosphonates [15, 16]. A Pudovik reaction is one of the crucial and highly valuables method for the hydrophosphonylation and C-P bond formation of aldehyde by addition of diethyl phosphate or triethyl phosphate. During past few years various methods have been developed for this synthesis. Basically, these methods are all similar, using different bases such as Et_3N, sodium alkoxide, KF on allumina, CsF, LDA, metal oxides, TMG, DBU, chiral catalyst/Ag_2CO_3 or using different acid catalysed such as $BF_3.Et_2O$, HCl, NH_4VO_3, TFA, $Ti(OPr_i)$, $NbCl_5$, $AlCl_3$, pyridinium perchlorate, camphor sulfonic acid and TMSCl[17] . All these methods activate either phosphate source or aldehyde for this conversion but majority operation suffer by using toxic solvents, expensive catalysts and exotic reaction conditions leading to formation of hazardous disposal waste.

As part of an exploration of the possibility of utilizing $Ba(OH)_2$ as a catalyst, herein we disclose synthesis of α-hydroxyphosphonates through hydrophosphonylation of aldehydes with diethyl phosphate (Scheme 1). Barium hydroxide has proved to be an efficient catalyst in organic synthesis because of its non-toxic nature, easy handling, low cost and high catalytic activity [18, 19]. Various organic transformations catalyzed by $Ba(OH)_2$ such as Wittig-Horner reaction [20], C-C bond formation [21, 22], C-N bond formation [23], preparation of cyclopentanol derivatives [24] etc. However, the utility of this catalyst for synthesis of α-hydroxyphosphonates has not been explored before.

Materials and Methods

All reactions were performed with commercially available reagents. All liquid reagents were distilled and dry before use. Melting points were determine by open tube capillary method and are uncorrected. IR spectra were obtained on Shimadzu FTIR-spectrometer (KBr Pellets), ^1H NMR spectra were recorded on a Bruker advance 400 spectrometer (400MHz) in $CDCl_3$ using TMS as internal reference and mass spectra were recorded under LCMS mode. The products were purified by recrystallisation using hexane/ethyl acetate mixture. All α-hydroxyphosphonates **2a-s** are characterized by IR, ^1H NMR and MS spectroscopy and identified by comparison of spectra and melting points those reported in the literature.

***General Procedure*:** An oven-dried flask was equipped with a magnetic stir bar were added aldehyde (1a-s) (1.0 mmol), barium hydroxide (10 mol %) and followed by dropwise addition of diethyl phosphate (1.1 mmol) (slight exotherm was observed) was stirred in solventless condition. The resulting mixture was stirred at room temperature for 4-10 min. (Table 2). When TLC analysis showed complete conversion, reaction mixture diluted with 10 ml DCM and separates the catalyst for reuse. The filtrate was concentrated under reduced pressure and resulting product wash with hexane or recrystallised by ethyl acetate-hexane mixture to furnish the analytical pure product (**2a-s**) with good to excellent yield.

Spectroscopic data:

Compound 2a: White solid with 96 % yield; m.p.= 76- 78 ^{0}C (lit.[25] 75- 77 ^{0}C); IR (KBr): γ_{max} 3248 (OH), 1209 (P=O), 1045 (P-O-C); ^1H NMR (400 MHz,$CDCl_3$): δ 7.49- 7.47 (m, 2H), 7.38- 7.25 (m, 3H),

ISSN: 2249 –4820
Chemistry & Biology Interface, 2012, 2, 5, 314-321

5,0(d, 1H, *J* = 11.2 Hz), 4.01- 3.95 (m, 4H), 1.24 (t, 3H, *J* = 7.2 Hz), 1.19 (t, 3H, *J* = 7.2); LCMS *m/z* (%): 245 (100) $[M + H]^+$.

Compound 2b: White solid with 96 % yield; m.p.= 86- 88 ^{0}C (lit.[25] 88- 90 ^{0}C); IR (KBr): γ_{max} 3242 (OH), 1212 (P=O), 1045 (P-O- C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 5.14 (dd, *J* = 4.4, 12.4 Hz, 1H), 4.23 (br s, 1H), 4.14-4.07 (m, 4H), 1.30- 1.25 (m, 6H); MS (ESI)*m/z:* 290 $[M + H]^+$, 272 $[M-OH]^+$, 244 $[MH- NO_2]$.

Compound 2c: White solid with 98 % yield; m.p.= 80- 82 ^{0}C (lit.[25] 81- 82 ^{0}C); IR (KBr): γ_{max} 3250 (OH), 1209 (P=O), 1048 (P-O-C); ^{1}H NMR (300 MHz,$CDCl_3$): δ 8.41 (s, 1H), 8.15 (d, 1H, *J* = 9 Hz), 7.80 (d, 1H *J* = 8.1 Hz), 7.50 (t, 1H *J* = 8.1 Hz), 5.14 (dd, 1H, *J* = 11.4 Hz), 4.18-4.09 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2, 3H); LCMS *m/z* (%): 290 (100) $[M + H]^+$.

Compound 2d: White solid with 82 % yield; m.p.= 114- 116 ^{0}C (lit.[25] 114- 116 ^{0}C); IR (KBr): γ_{max} 3220 (OH), 1210 (P=O), 1030 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 8.17 (d, 2H, *J* = 8.0 Hz), 7.81 (t, 1H, *J* = 7.6 Hz), 7.52 (t, 1H, *J* = 8.0 Hz), 5.14 (dd, *J* = 4.8, 11.2 Hz, 1H), 4.17 (br s, 1H), 4.17-4.09 (m, 4H), 1.28 (t, 3H, *J* = 6.8 Hz), 1.25 (t, 3H, *J* = 6.8); MS (ESI) *m/z:* 290 $[M + H]^+$.

Compound 2e: White solid with 96 % yield; m.p.= 76- 78 ^{0}C; IR (KBr): γ_{max} 3010 (OH), 2245 (CN),1234 (P=O), 1037 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.66-7.60 (m, 4H), 5.12 (dd, *J* = 4.8, 12 Hz, 1H), 4.77 (br s, 1H), 4.12-4.05 (m, 4H), 1.29-1.23 (m, 6H); LCMS *m/z* (%)270 (100) $[M + H]^+$.

Compound 2f: White solid with 91 % yield; m.p.= 66- 68 ^{0}C (lit.[25] 67- 68 ^{0}C); IR (KBr): γ_{max} 3300 (OH), 1231 (P=O), 1048 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.41 (d, 2H, *J* =8.4 Hz,), 7.32 (d, 2H, *J* = 8.4Hz), 4.98 (d, 1H, *J* = 10.8 Hz), 4.08-4.01 (m, 4H), 1.26 (t, 3H, *J* = 6.8), 1.25 (t, 3H, *J* = 7.2); MS (ESI) *m/z* (%): 279 (100) $[M + H]^+$, 261 (70) $[M-Cl]^+$.

Compound 2g: White solid with 88 % yield; m.p.= 76- 78 ^{0}C (lit.[25] 74- 75 ^{0}C); IR (KBr): γ_{max} 3280 (OH), 1228(P=O), 1045 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.71 (d, 1H, *J* = 7.6 Hz), 7.36- 7.23 (m, 3H), 5.54 (d, 1H, *J* = 11.2 Hz), 4.19-3.96 (m, 4H), 1.29 (t, 3H, *J* = 7.2 Hz,), 1.20 (t, 3H, *J* = 7.2); MS (ESI) *m/z* (%): 279 (100) $[M + H]^+$.

Compound 2h: White solid with 96 % yield; m.p.= 70- 72 ^{0}C; IR (KBr): γ_{max} 3274 (OH), 1225(P=O), 1041 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.66 (d, 1H, *J* = 7.6 Hz), 7.41(d, 1H, *J* = 8Hz), 7.24 (t, 1H, *J* = 8 Hz), 5.58 (d, 1H, *J* = 11.6 Hz), 4.82 (br s, 1H), 4.19-3.98 (m, 4H), 1.31 (t, 3H, *J* = 7.2 Hz,), 1.21 (t, 3H, *J* = 7.2); LCMS *m/z* (%):313 (100) $[M^+]$.

Compound 2i: White solid with 94 % yield; m.p.= 90- 92 ^{0}C (lit.[25] 90- 91 ^{0}C); IR (KBr): γ_{max} 3222 (OH), 1208 (P=O), 1045 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.67 (d, 1H, *J* = 7.6 Hz), 7.39 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 3H), 5.48 (d, 1H, *J* = 12 Hz), 4.75 (br s, 1H), 4.18-4.02 (m, 4H), 1.31 (t, 3H, *J* = 7.2 Hz), 1.23 (t, 3H, *J* = 7.2 Hz); LCMS *m/z* (%): 313 (100) $[M^+]$.

Compound 2j: White solid with 92 % yield; m.p.= 92- 94 ^{0}C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.32 (d, 2H, *J* = 8.4 Hz), 7.16 (t, *J* = 8 Hz, 3H), 5.81 (d, 1H, *J* = 19.6 Hz), 4.27-3.93 (m, 4H), 3.044 (br s, 1H),1.35 (t, 3H, *J* = 6.8 Hz,), 1.15 (t, 3H, *J* = 6.8 Hz); LCMS *m/z* (%): 313 (100) $[M^+]$.

Compound 2k: White solid with 92 % yield; m.p. 64- 66^{0}C; IR (KBr): γ_{max} 3242 (OH), 1231(P=O), 1028 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.48 (d, 2H, *J* =8.4

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 314-321

Hz), 7.31 (d, 2H, *J* = 8.4 Hz), 4.98 (d, 1H, *J* = 10.0 Hz,), 4.1-3.99 (m, 4H), 1.26 (t, 3H, *J* = 7.2 Hz), 1.25 (t, 3H, *J* = 7.2 Hz); MS (ESI) *m/z* (%): 323 (100) $[M^+]$, 305 (42) $[M\text{- }OH]^+$.

Compound 2l: White solid with 84 % yield; m.p.= 62- 64 ^{0}C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.71 (d, 1H, *J* =8.4 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.32 (t, 1H, *J* =7.2 Hz), 7.17 (t, 1H, *J* = 7.2 Hz), 4.53 (d, 1H, *J* = 10.0 Hz,), 4.21-3.92 (m, 4H), 1.31 (t, 3H, *J* = 7.2 Hz) 1.21 (t, 3H, *J* = 7.2 Hz); LCMS *m/z* (%): 323 (100) $[M^+]$.

Compound 2m: White solid with 94 % yield; m.p.= 64- 66 ^{0}C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.48-7.45 (m, 2H), 7.03 (t, 2H, *J* = 8.4 Hz), 4.99 (d, 1H, *J* = 10.0 Hz,), 4.07-3.96 (m, 4H), 1.29-1.21 (m, 6H); MS (ESI) *m/z* (%): 263 (100) $[M^+]$, 245 (67) $[M\text{-}OH]^+$.

Compound 2n: White solid with 90 % yield; m.p.= 72- 74 ^{0}C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.36-7.12 (m, 3H), 6.99 (t, 1H, *J* = 7.2 Hz), 5.05 (d, 1H, *J* = 13.0 Hz,), 4.13-4.0 (m, 4H), 1.34-1.12 (m, 6H); MS (ESI) *m/z* (%): 263 (100) $[M^+]$, 245 (36) $[M\text{-}OH]^+$.

Compound 2o: White solid with 81 % yield; m.p.= 120- 122 ^{0}C (lit.[25] 120- 121 ^{0}C); IR (KBr): γ_{max} 3245 (OH), 1220 (P=O), 1045 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.41 (dd, 2H, *J* = 1.6, 8.4 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 4.93 (d, 1H, *J* = 9.6 Hz), 4.09-3.99 (m, 4H), 3.81 (s, 3H), 1.26 (t, 3H, *J* = 7.2), 1.20 (t, *J* = 7.2, 3H); MS (ESI) *m/z* (%):275 (25) $[M + H]^+$, 257 (100) $[M\text{-}OH]^+$.

Compound 2p: White solid with 80 % yield; IR (KBr): γ_{max} 3244 (OH), 1225(P=O), 1030 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.07 (s, 1H), 7.00 (d, 1H, *J* = 8.0 Hz), 6.84 (d, 1H, *J* = 8.4 Hz), 4.93 (d, 1H, *J* = 10.0 Hz,), 4.08-4.0 (m, 4H), 3.88 (s, 3H), 3.89 (s, 3H), 1.27 (t, 3H, *J* = 7.2 Hz) 1.21 (t, 3H, *J* = 7.2 Hz); MS (ESI) *m/z* (%): 305 (38) $[M + H]^+$, 287 (100) $[M\text{- }OH]^+$.

Compound 2q: White solid with 76 % yield; m.p.= 104- 106 ^{0}C (lit.[25] 105- 106 ^{0}C); IR (KBr): γ_{max} 3241 (OH), 1209 (P=O), 1030 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$) 7.41-7.23 (m, 5 H), 6.76 (dd, 1H, *J* = 4.0, 15.2 Hz), 6.34-6.27 (m, 1H), 4.64-4.69 (m, 1H), 4.24-4.06 (m, 4H), 1.33 (t, 3H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz); MS (ESI) *m/z* (%): 271(25) $[M + H]^+$, 253 (100) $[M\text{-}OH]^+$.

Compound 2r: Colorless oil[26] with 72% yield; IR (KBr): γ_{max} 3271 (OH), 1237 (P=O),1048 (P-O-C); ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.32- 7.30 (m, 1H), 7.20–7.18 (m, 1H), 7.01–6.99 (m, 1H), 5.20 (d, 1H, *J*= 10.8 Hz), 4.28–4.0 (m, 4H), 1.28 (t, 3H, *J*= 6.8 Hz), 1.25 (t, 3H, *J*= 6.8Hz). MS (ESI) *m/z* (%): 351 (94) $[M + H]^+$, 233 (100) $[M\text{- }OH]^+$.

Results and discussions

For the purpose of optimization of the experimental conditions, we choose coupling between benzaldehyde (**1a,** Table 2) with diethyl phosphate under solvent free conditions (Scheme 1) as a model reaction. Screening of various catalysts examined at room temperature, (Table 1) including acidic and basic. Firstly, no desirable product could be detected when a mixture of benzaldehyde (1 mmol), and diethyl phosphate (1.2 mmol) was stirred at room temperature for 12 hr in the absence of catalyst (Table 1, entry 1), indicating a catalyst must be needed for the Pudovik reaction. Various acid catalysts such as $BaCl_3$, LiCl, SiO_2, SiO_2-MoO_3 (Table 1, entry 2-5, 20 mol% each) were applied for the reaction but desired product obtained is less than 20% yield. To address this problem, we screened different bases

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Chemistry & Biology Interface, 2012, 2, 5, 314-321

such as DBU, K_2CO_3, K_3PO_4, $CsCO_3$ and $Ba(OH)_2$ (Table 1, entry 6-10, 20 mol% each) and found that $Ba(OH)_2$ was most efficient base (entry 10).

In this reaction, during the addition of diethyl phosphate to mixture of benzaldehyde and $Ba(OH)_2$ slight exotherm was observed. Furthermore, We investigated the catalytic amount required for the reaction and found that 10 mol % of $Ba(OH)_2$ (Table 1, entry 11) gives excellent yield 96% only in 5min. While less amount of catalyst 5 mol % (Table 1, entry 12) shows slight decrease in yield.

Applying optimized reaction conditions to broad range of structurally functionalized aldehydes to check the generality of this procedure (Scheme 2). Diethyl phosphate accelerates the rate of reaction and provides a library of α-hydroxy phosphonates with a variety of substituents such as electron withdrawing, electron donating, halogens, conjugated C-C double bond, and heterocyclic moieties. The corresponding α-hydroxyphosphonates were obtained in good to excellent yield and the results are summarized in Table 2. The established mechanism of this reaction involves nucleophilic attack of a dialkyl phosphate anion, forming by tautomeric forms between phosphonate and phosphite of dialkyl phosphate, on electrophilic carbonyl carbon of aldehyde under solvent free conditions, and leading to the synthesis of α-hydroxyphosphonates. Electron withdrawing substituents at ortho-, meta-, and para-position of the aryl ring reacts very faster and completed reaction within 5 min. with excellent yield (Table 2, entries 1b-1e). Similarly, halogenated aldehydes also smoothly reacted and give corresponding α-hydroxyphosphonates in higher yield within 5-8 min. (Table 2, entries 1f-1n). Electron rich substituents (Table 2, entries 1o and1p) as well as sterically demanding substrate (Table 2, entries 1d, 1g-1j and 1l) did not hamper the reactivity. While, heterocyclic substrate required some excess time as compared with others and gives moderate yield (Table 2, entries 1r-1s). In general, the reactions are very clean; no side product was obtained and easy recovery of the catalyst from the reaction mixture. The reusability of barium hydroxide as a catalyst is also checked (Table 3) for 3-nitro benzaldehyde (Table 1, entry 1c**)** and found to be without loss of its activity up to four run. Thus, barium hydroxide can be successfully implemented as a heterogeneous renewable catalyst for the synthesis of α-hydroxyphosphonates. Most significantly, the whole operation does not involve any acidify or basify condition stage for isolation of product. All compounds were characterized and confirmed by IR, ^1H NMR, Mass and melting points compared with those reported methods.

Conclusion

In conclusion, we have developed a synthetically useful, operationally simple, greener protocol for the synthesis of α-hydroxyphosphonates that allows for the preparation of a variety of important intermediates. Important to the success of this methodology was to inhibit the use of solvent by using barium hydroxide as a catalyst. This method is applicable for aromatic, hetero-aromatic and sterically hindered aldehydes. The products were isolated in high purity with good to excellent yield (70- 98 %).

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ISSN: 2249 –4820

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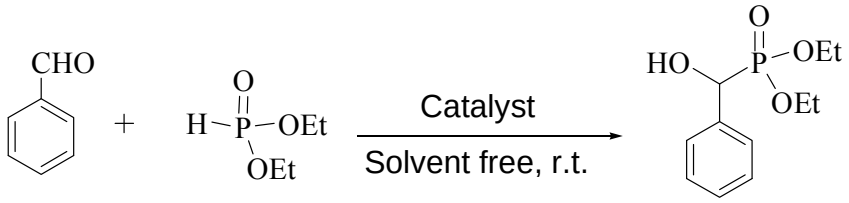
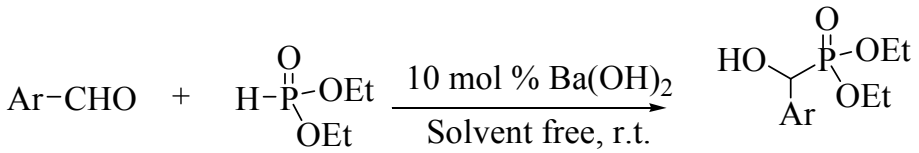


Scheme 1. Synthesis of diethyl 1-hydroxy phenylmethylphosphonate.

Table 1 Screening of various catalyst under solvent free conditions [a]

Entry	Catalyst	Mole %	Time	Yield[b] %
1	No catalyst	--	12 hr	No reaction
2	$BaCl_3$	20	24 hr	No reaction
3	LiCl	20	24 hr	No reaction
4	SiO_2	20	12 hr	< 20
5	MoO_3-SiO_2	20	12 hr	< 20
6	DBU	20	2 hr	76
7	K_2CO_3	20	60 min.	90
8	K_3PO_4	20	2 hr	43
9	$CsCO_3$	20	22 min.	92
10	$Ba(OH)_2$	20	5 min.	96
11	$Ba(OH)_2$	10	5 min.	96
12	$Ba(OH)_2$	05	5 min.	94

[a] Reaction condition: 2 mmol aldehyde, 2.2 mmol diethyl phosphate, catalyst, r.t.
[b] Isolated purified product.



1a-s **2a-s**

Scheme 2. Synthesis of α-hydroxyphosphonates under solvent free conditions.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 314-321

Table 2 Synthesis of various α-hydroxyphosphonates under solvent free conditions [a]

Entry	Ar	Time (min.)	Product [b]	Yield[c] %
1a	C_6H_5-	5	**2a**	96
1b	4-$NO_2C_6H_4$-	4	**2b**	95
1c	3-$NO_2C_6H_4$-	4	**2c**	98
1d	2-$NO_2C_6H_4$-	5	**2d**	82
1e	4-CN C_6H_4-	4	**2e**	96
1f	4-ClC_6H_4-	5	**2f**	91
1g	2-ClC_6H_4-	8	**2g**	88
1h	2,3-Cl_2 C_6H_3-	6	**2h**	96
1i	2,4-Cl_2 C_6H_3-	5	**2i**	94
1j	2,6-Cl_2 C_6H_3-	10	**2j**	92
1k	4-BrC_6H_4-	7	**2k**	92
1l	2-BrC_6H_4-	8	**2l**	84
1m	4-FC_6H_4-	5	**2m**	94
1n	3-FC_6H_4-	6	**2n**	90
1o	4-$CH_3OC_6H_4$-	5	**2o**	81
1p	3,4-$(CH_3O)_2C_6H_3$-	10	**2p**	80
1q	C_6H_5CH=CH-	8	**2q**	76
1r	2-Thiophene	8	**2r**	72
1s	4- Pyridyl	6.5	**2s**	70

[a] Reactions Conditions: aldehyde (1mmol), diethyl phosphate (1.2 mmol), 10mol % $Ba(OH)_2$,r.t.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 5, 314-321

[b] All compounds were characterized by using IR, ^{1}H NMR and MS and mp.

[c] Isolated yield.

Table 3. Recovery and reuse of $Ba(OH)_2$ in the synthesis of **2c** (Table 2, entry 1c).

$Ba(OH)_2$	Fresh	Run-I	Run-II	Run-III	Run-IV
Yield (%)[a]	98	97	96	95	95

[a] Isolated pure yield.

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