TBAI/TBHP mediated oxidative cross coupling of aryl alkyl ketones with H-phosphonates and H-phosphine oxides in water: facile access to ketol phosphates and phosphinates

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TBAI/TBHP mediated oxidative cross coupling of aryl alkyl ketones with H-phosphonates and H-phosphine oxides in water: facile access to ketol phosphates and phosphinates

G. Saidulu, R. Arun Kumar, T. Anitha, P. Santhosh Kumar and K. Rajender Reddy*

Inorganic and Physical Chemistry Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Telangana State, Hyderabad – 500 007, India.

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ABSTRACT

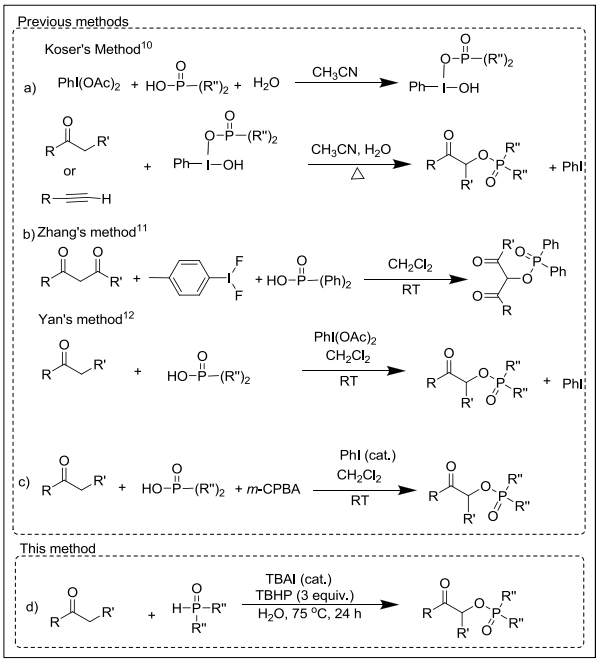
A metal free cross coupling of aryl alkyl ketones with alkyl/aryl H-phosphonates and H-phosphine oxides using tetrabutylammonium iodide (TBAI) catalyst in presence of *tert*-butyl hydroperoxide (TBHP) as terminal oxidant in aqueous media is developed. This new approach offers a direct and convenient route to access a wide range of ketol phosphates and phosphinates in moderate to good yields.

Direct activation of C-H bonds and subsequent coupling with carbon and heteroatom based pro-nucleophiles to generate new carbon-carbon (C-C) and carbon-heteroatom (X= N, O, P) bonds under oxidative conditions have emerged as one of the most reliable and robust tools in modern synthetic organic chemistry. Since, this approach avoids the pre-formed precursors and thus provides a direct, atom-economical and environmentally benign route to synthesize biologically relevant organic molecules. Over the past decade, tremendous progress has been made on oxidative cross coupling methodology using variety of coupling partners and catalytic systems.[1] Generally, these reactions are furnished using transition metal catalysts and oxidants such as molecular oxygen (O_2), hydrogen peroxides and organic peroxides). Moreover, numerous transition-metal free oxidative coupling methods have also been reported using stoichiometric oxidants such as hypervalent iodine reagents,[2] 2,3-dichloro-5,6-dicyanohydroquinone (DDQ),[3] benzoylperoxide (BPO)[4] and others.[5] However, the problems associated with the above methods are use of expensive metals, tedious procedures to remove metal impurities and most importantly, the release of large amount of undesired by-product by the high mass stoichiometric oxidants.

In recent years, iodine or iodide salts are recognized as an ideal substitute to transition metal catalysts and organo hypervalent iodine reagents. Notably, the combination of tetrabutylammonium iodide (TBAI) and *tert*-butyl hydroperoxide (TBHP) has found to be an attractive metal-free catalytic system, especially in oxidative cross coupling reactions owing to its mild, easy removable, high efficient and eco-friendly characteristics.[6]

* Corresponding author. Tel.: +91-040-2719-1532; fax: +91-040-27160921; e-mail: rajender@iict.res.in; rajenderkallu@yahoo.com.

In particular, ketol phosphates are well-known biologically relevant organic compounds which are used as sugar analogues and important precursor for the synthesis of phospholipids and nucleotides.[7] Several synthetic methods are documented in the literature for the preparation of this moiety.[8-12] However, most of the methods are devoted to the oxidative coupling strategy involving pre-formed or *in situ* generated organo hypervalent iodine reagents (Scheme 1).[9-12]



Scheme 1 Different approaches to prepare ketol phosphates.

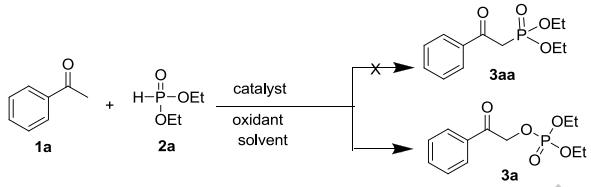
Koser and co-workers demonstrated the pre-formed iodine (III) phosphate promoted α-phosphoryloxylation of ketones[10a] and they have also described the regio-specific conversion of terminal alkynes to ketol phosphates using iodine (III) phosphate reagent (Scheme 1, **a**).[10b] Recently, Zhang developed the *p*-iodotoluene difluoride (*p*-Tol-IF_2) mediated α-phosphoryloxylation of 1,3-dicarbonyl compounds with diphenylphosphate (Scheme 1, **b**).[11] Yan's group reported an efficient α-phosphoryloxylation of ketones with phosphates to generate ketol phosphates (Scheme 1, **c**) in the presence of (diacetoxyiodo)benzene.[12a] Very recently, the same group also developed an effective catalytic method for the oxidative coupling between ketones and phosphates using iodobenzene (PhI) as catalyst and *meta*-chloroperbenzoic acid (*m*-CPBA) as terminal oxidant (Scheme 1, **c**).[12b] However, most of these methods have certain drawbacks such us limited substrate scope and release of massive by-product from the pre-formed hypervalent iodine compounds at the end of the reaction, thus limiting its practical application. Therefore, still there is a demand for the development of efficient and environmentally benign methods to access ketol phosphate.

Over the past few years, our group has been focusing on the synthetic usefulness of transition-metal free catalysts particularly iodine or iodide salt for various organic transformations.[13] In continuation of our efforts, herein we wish to describe a simple, convenient and direct method for the synthesis of ketol phosphates through oxidative coupling of aryl methyl ketones with H-phosphonates and H-phosphine oxides using TBAI as a catalyst and TBHP as an oxidant in aqueous media.

Recent literature data reveals that there is renewed interest on H-phosphonates in cross coupling chemistry.[14] Very recently we have shown application of H-phosphonates as a cross-coupling partners in the synthesis of substituted 3,4-dihydroquinazolines.[15] To extend the scope of H-phosphonates, it was originally intended to look at the feasibility of cross coupling between acetophenone (**1a**) with H-phospahonate (**2a**) i.e diethyl phosphite to generate β-keto phosphonate (**3aa**) under metal and metal-free conditions (Table 1). No product was observed with I_2, KI, copper and iron catalysts (Table 1, entries 1-5). To our surprise, unexpected ketol phosphate was selectively formed in less than 10% isolated yield with TBAI and the desired β-keto phosphonate (**3aa**) could not observe under this condition (Table 1, entry 6). Furthermore, the formation of **3a** was confirmed by spectral analysis (H^1, P^{31} NMR and LC-MS) and spectral datas were consistent with reported one.

Encouraged by this preliminary result, we did further investigation to achieve optimal reaction conditions for the formation of ketol phosphate selectively and the results are summarized in table 1. Among different solvents tested, water (H_2O) was best solvent media for this reaction (Table 1, entries 7-9). Other oxidants such hydrogen peroxide (H_2O_2), potassium persulfate ($K_2S_2O_8$) and di-*tert*-butyl peroxide (DTBP) could not improve the efficiency of the reaction (Table 1, entries 11-13). Control experiments clearly reveal that both the catalyst (TBAI) and oxidant (TBHP) play crucial role in this oxidative transformation (Table 1, entries 14 and 15). The yield of the desired product **3a** was 17%, when the reaction performed in 50 ^oC (Table 1, entry 16). Similarly, the isolated yield of **3a** was decreased to 38% when amount of TBHP reduced from 3 equivalents to 1.5 equivalents (Table 1, entry17). Finally, treatment of 2 equivalents acetophenone (**1a)** with 1 equivalent of diethyl phosphonate (**2a)** in the presence 20 mol% of TBAI and 3 equivalents of TBHP in 2 mL of water at 75 ^oC for 24 hours was found to be the best conditions for this oxidative transformation (Table 1, entry 9).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield(%)[b] 3a
1	I_2	TBHP in H_2O	DCE	N.D
2	KI	TBHP in H_2O	DCE	N.D
3	CuI	TBHP in H_2O	DCE	N.D
4	$Cu(OAc)_2$	TBHP in H_2O	DCE	N.D
5	$FeCl_2$	TBHP in H_2O	DCE	N.D
6	TBAI	TBHP in H_2O	DCE	<10
7	TBAI	TBHP in H_2O	CH_3CN	<10
8	TBAI	TBHP in H_2O	EtOAc	<10
9	**TBAI**	**TBHP in H_2O**	**H_2O**	**56**
10	TBAI	TBHP in H_2O	H_2O	13
11	TBAI	H_2O_2	H_2O	36
12	TBAI	$K_2S_2O_8$	H_2O	N.D
13	TBAI	DTBP	H_2O	N.D
14	TBAI	-	H_2O	N.D
15	-	TBHP in H_2O	H_2O	N.D
16	TBAI	TBHP in H_2O	H_2O	17[c]
17	TBAI	TBHP in H_2O	H_2O	38[d]

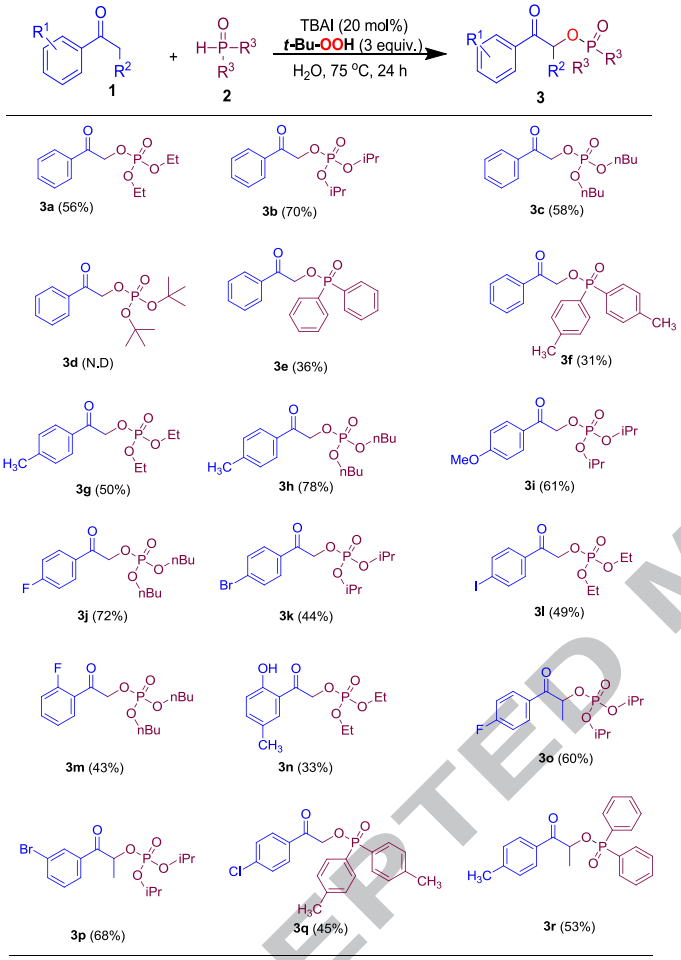
[a]Reaction conditions: (i) Acetophenone **1** (2 mmol), diethylphosphite **2** (1 mmol), TBAI (20 mol%), 70 wt% TBHP in H_2O (3 equiv.), H_2O (2 mL), 75 ^oC, 24 h.
[b]Isolated yield of **3a** after SiO_2 column chromatography,
[c]reaction performed at 50 ^oC.
[d]1.5 equivalents TBHP used.

After establishing the optimal reaction conditions, the scope of the substituted acetophenones and H-phosphonates were studied and the results are summarized in table 2. Acetophenone (**1a**) was reacted with other aliphatic H-phosphonates such as di-isopropyl and di-butyl phosphonates and afforded the corresponding products **3b** and **3c** in 70% and 58% isolate yields respectively. Under this standard condition, **1a** could not react with di-*tert*-butyl phosphonate, which may be because of steric influence of phosphonate (Table 2, **3d**). Whereas diaryl H-phosphine oxides i.e. diphenyl and di-*p*-tolyl H-phosphine oxides provided the corresponding ketol phosphinate products **3e** and **3f** in lower yields. Aryl group of acetophenone containing electron donating groups (methyl and methoxy) coupled with dialkyl phosphonates and afforded the corresponding products in moderate to good isolated yields (Table 2, **3g-3i**).

Gratifyingly, halogenated acetophenones such as fluro, bromo and iodo acetophenones worked well under this standard condition and gave the desired ketol phosphates **3j**, **3k**, **3l** and **3m** in satisfactory yields (Table 2, **3j-3m**). Reaction of 5-methyl-2-hydroxy acetophenone with diethyl phosphonate afforded the product **3n** in 33% isolated yield. In addition, propiophenones were also examined to react with dialkyl phosphonates under this

standard condition and the representative products were afforded in moderate yields (Table 2, **3o** and **3p**). In addition, H-phosphine oxides were tried to couple with *p*-chloro-acetophenone and propiophenone and the corresponding ketol phosphinates **3q** and **3r** were obtained in satisfactory isolated yields (Table 2, **3q** and **3r**). .

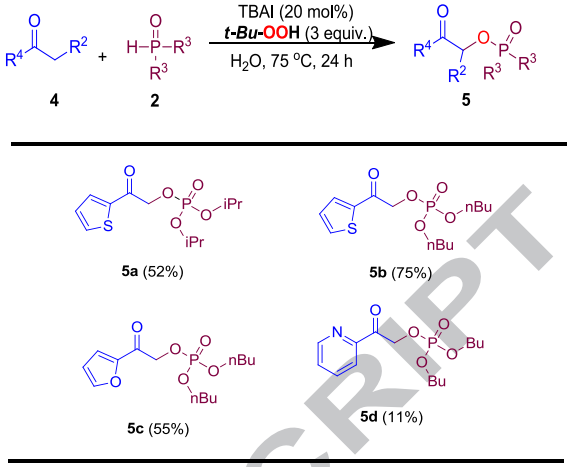
Table 2 Scope of aryl alkyl ketones couplinf reaction with H-phosphonates and H-phosphine oxides[a]



[a]Reaction conditions: (i) Aryl alkyl ketone **1** (2 mmol), dialkyl H-phosphonates or diaryl H-phosphine oxide **2** (1 mmol), TBAI (20 mol%), 70 wt% TBHP in H_2O (3 equiv.), H_2O (2 mL), 75 °C, 24 h. [b]Numbers in parentheses are isolated yields of the products after SiO_2 column chromatography.

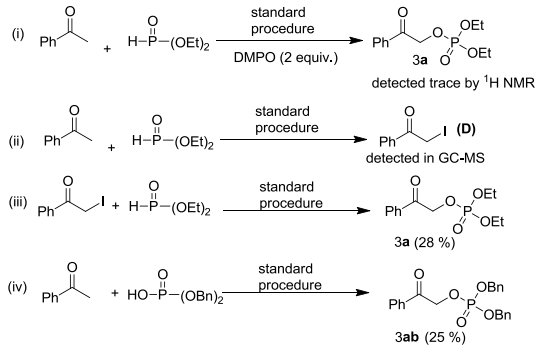
Furthermore, scope of the reaction was extended to heteroaryl methyl ketones and the representative results are shown in table 3. Thiophene methyl ketone coupled smoothly with di-isopropyl and di-butyl phosphonates under this optimized reaction conditions and the products **5a** and **5b** were obtained in moderate to good isolated yields (Table 3, **5a, 5b**). Furyl methyl ketone was also oxidatively coupled with dibutyl phosphonate to accomplish ketol phosphate **5c** in 55% isolated yield (Table 3, **5c**). The isolated yield of the ketol phosphate was very low, when the reaction was performed between pyridyl methyl ketone and di-butyl phosphonate (Table 3, **5d**).

Table 3 Scope of heteroaryl methyl ketones[a,b]



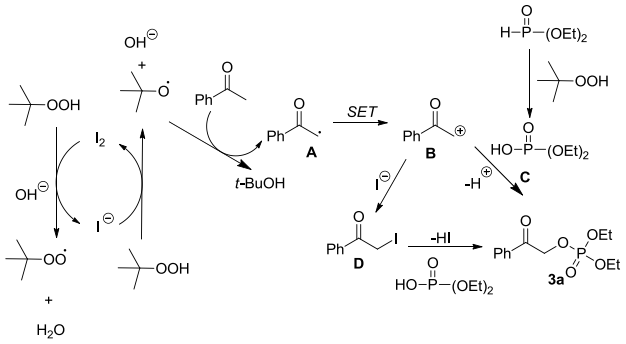
[a]Reaction conditions: (i) Heteroaryl methyl ketone **4** (2 mmol), dialkylphosphonate **2** (1 mmol), TBAI (20 mol%), 70 wt% TBHP in H_2O (3 equiv.), H_2O (2 mL), 75 °C, 24 h.
[b]Numbers in parentheses are isolated yields of the products after SiO_2 column chromatography.

To gain mechanistic insight of this oxidative transformation four observations were made experimentally as shown in scheme 2: (i) Only trace amount of product **3a** formed in the presence of radical scavenger 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO). (ii) Formation of small amount of α-iodoacephenone by GC-MS analysis of crude reaction mixture. (iii) Formation of product with pre-synthesized α-iodoacetophenone. (iv) Formation of corresponding product with dibenzyl hydrogen phosphate ($Bn_2PO(OH)$ (see supporting information).



Scheme 2 Experiments for the mechanistic study.

The exact mechanism for the product formation is not clear at present stage. However, based on the above observations as well as from the previous reports,[16] a plausible mechanism for this oxidative transformation is illustrated in scheme 3. Initially, TBHP is converted into tertiary butoxide radical catalytically with an aid of iodide anion and this radical trap the hydrogen (H) from the acetophenone and generates radical cation **A.**[16a] Subsequently, the hypothetic radical cation **A** is converted into carbocation intermediate **B** *via* oxidative single electron transformation (SET).[16b] After that there are two possible ways for the conversion of carbocation into final product **3a**: (i) The carbocation **B** can directly undergo nuclephilic addition reaction with diethyl hydrogen phosphate **C,** which is formed *in situ* by the direct oxidation of diethyl phosphite with TBHP.[16c] (ii) The carbocation **B** can be also attacked with iodide anion to form α-iodo acetophenone (**D**) and subsequently iodide is substituted by the diethyl hydrogen phosphate to yield the final product **3a**.



Scheme 3 Plausible mechanism.

In conclusion, we have demonstrated a metal-free and environmentally benign route for the synthesis of ketol phosphates and phosphinates *via* direct oxidative cross coupling between aryl alkyl ketones and H-phosphonates/H-phosphine oxides. Importantly, this method exhibits good compatibility with various phosphonates/phosphine oxides and avoids the use of hazardous reagents. It is worth noting that the reaction proceeds in water under mild conditions using commercially available catalyst (TBAI) and oxidant (TBHP). Furthermore, investigations on the reaction mechanism and to expand the scope of these reactions are underway in our laboratory.

General procedure of Ketol Phosphates

A 70 wt% *tert*-butyl hydroperoxide solution in H_2O (TBHP, 3.0 mmol), was added dropwise for 15 minutes into the mixture of acetophenone derivatives (2.0 mmol), TBAI (20 mol%) and dialkyl or diaryl phosphite or H-phosphine oxide (1.0 mmol) in water (H_2O, 2.0 mL). The resulting mixture was stirred at 75 °C for 24 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the resulting solution was cooled to room temperature. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether/ethylacetate as an eluent and the products were charecterised by ^1H, ^{13}C, ^{31}P NMR, IR, ESI and HRMS analysis. **3a** (153 mg, 56%) *Diethyl 2-oxo-2-phenylethyl phosphate:* IR 2983, 2928, 2858, 1708, 1598, 1449, 1373, 1265, 1116, 1029, 975, 855, 756, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ δ 7.90 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 5.33 (d, J = 9.8 Hz, 2H), 4.25-4.18 (m, 4H), 1.37 (t, J = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 133.8, 128.8, 127.6, 68.6 (d, J = 4.5 Hz), 64.3 (d, J = 5.4 Hz), 16.0 (d, J = 7.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ -0.75; MS (ESI) m/z = 295 $(M+Na)^+$; (ESI-HRMS) calculated for $C_{12}H_{17}O_5NaP$ $(M+Na)^+$: 295.07058, found: 295.07059.

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Highlights

- Transition metal free oxidative cross coupling reaction is demonstrated.
- The present protocol offers direct and facile access to ketol-phosphates and phosphinates.
- Performing the reactions in aqueous media make this methodology greener.

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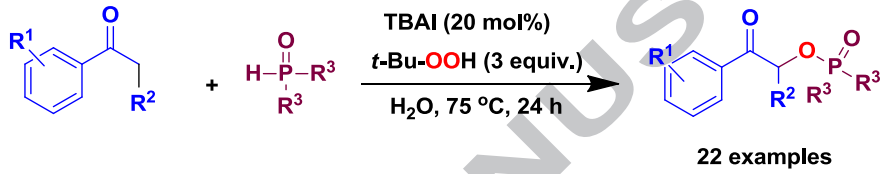

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