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Metal-Free Oxidative Cleavage of C-C bond in α-Hydroxy-β-oxophosphonates

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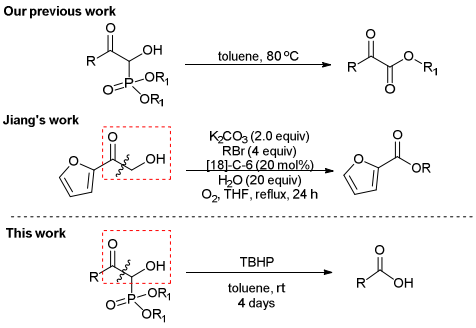
Satyanarayana Battula, [a,b] Atul Kumar, [a,b] and Qazi Naveed Ahmed[a,b]*

The potential of TBHP to promote oxidative hydroxylation of α-hydroxy-β-oxophosphonates (HOP) through C(CO)–C bond Cleavage is described. This cleavage, as depicted in mechanism is expected through an isomer of HOP that reacts with TBHP to generate acids.

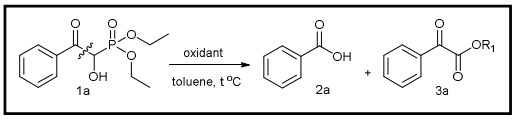
The C-C bond cleavage is a challenging field and has immense importance in modern organic chemistry owing to its high thermodynamic stability and uncontrollable selectivity.[1] In past few decades, numerous unprecedented carbon–carbon bond cleavage methods have been developed.[1] Despite plethora of methods have been accomplished in the oxidative cleavage of C-C bonds, the use of toxic metals under harsh conditions in combination with other additives may produce large amount of byproducts which perhaps limits its applications.[1,2] Therefore, the discovery of a metal-free method to achieve unique C-C bond cleavage is still desirable for various synthetic transformations.[3] Recently, we described a novel approach for generation of biologically valuable α-hydroxy-β-oxophosphonates (HOP) through 2-oxo promoted hydrophosphonylation of H-phosphonates.[4] The unique capability of α-hydroxy-β-oxophosphonates was further exploited to synthesize 2-oxoesters under catalyst free condition (Scheme 1). As an advancement in application of HOP, our further endeavours to evaluate its features by its new linkage, helped to develop a metal-free oxidative C(CO)-C bond cleavage in HOP. In 2012, Jiang. X and his co-workers also reported cleavage of α-hydroxyketones under transition metal-free condition.[5] In comparison to his work; we explored TBHP as a reagent of choice for generation of acids through oxidative hydroxylation of HOP.

We commenced our studies by the reaction of diethyl (1-hydroxy-2-oxo-2-phenylethyl)phosphonate **1a** (1.0 mmol) with 1.2 mmol of TBHP in toluene at 80 °C for 7 h. Fortunately, we obtained benzoic acid **2a** in low yield (10%), along with α-oxoester **3a** (entry 1, Table 1). The outcome of the benzoic acid **2a** was apparently caused by the oxidative cleavage of C-C bond in **1a**, and it ultimately prompted us to optimize the reaction conditions for enrichment of the desired product **2a**. For this we initially screened our reaction at different tempera-



Scheme 1. Summary of this work

Table 1. Optimization of the reaction[a]



entry	Oxidant	t (°C)	time	Yield (%)[b] 2a	3a
1.	TBHP (1.2 mmol)	80	7 h	10	70
2.	TBHP (1.2 mmol)	60	7 h	12	56
3.	TBHP (1.2 mmol)	rt	7 h	-	-
4.	TBHP (1.2 mmol)	rt	4 days	52	<5
5.	TBHP (1.5 mmol)	rt	4 days	61	<5
6.	TBHP (2 mmol)	rt	4 days	92	-
7.	TBHP (2.2 mmol)	rt	4 days	92	-
8.	IBX (2 mmol)	rt	4 days	15	<5
9.	$K_2S_2O_8$ (2 mmol)	rt	4 days	41	10
10.	Oxone (2 mmol)	rt	4 days	54	<10
11.	H_2O_2 (2 mmol)	rt	4 days	47	-
12.	NBS (2 mmol)	rt	4 days	-	-

[a]Reaction conditions: HOP **1a** (1.0 mmol), TBHP (2.0 mmol) and toluene (2 mL) at room temperature for 4 days; [b] isolated yields are given

[a] *Medicinal Chemistry Division, Indian Institute of Integrative Medicine (IIIM), Jammu, India-180001.*
[b] *Academey of Scientific and Innovative Research (AcSIR Fax: +91-1912569333), 2-Rafi Marg, New Delhi, India.*
* naqazi@iiim.ac.in, IIIM/1831/2015.

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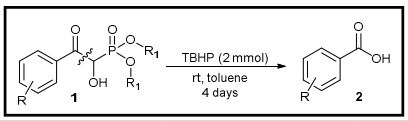
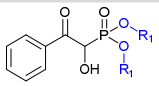
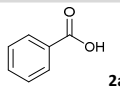
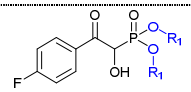
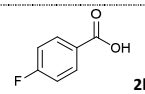
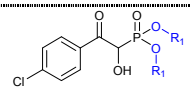
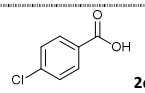
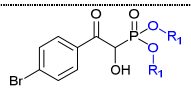
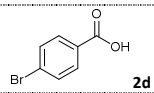
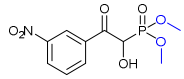
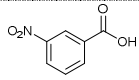
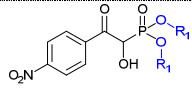
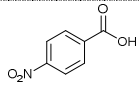
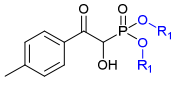
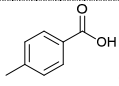
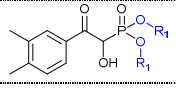
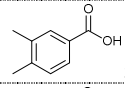
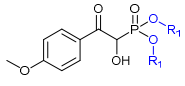
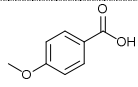
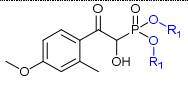
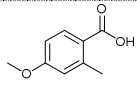
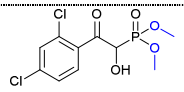
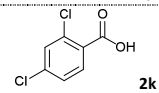
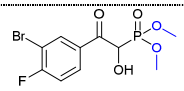
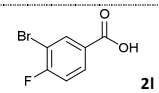
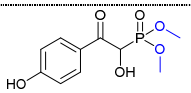
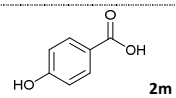
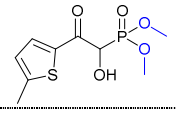
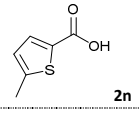
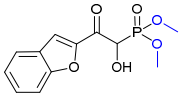
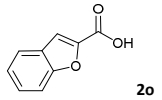
tures/ time (entry 1-4). We were gratified to see that the concentration of benzoicacid was enhanced at room temperature when stirred for 4 days (52%, entry 4). After this initial result, we attempted optimization of the reaction at varied concentrations of TBHP at room temperature (entry 5-7). We discovered **2a** could be achieved exclusively in 92% yield when the reaction was conducted at room temperature between **1a** (1.0 mmol) and TBHP (2.0 mmol) in 2 mL of toluene for 4 days (entry 6). Furthermore, a series of reactions were conducted with different oxidizing agents, including IBX, $K_2S_2O_8$, oxone, H_2O_2, NBS; but no one procured better yields than TBHP (entry 8-12). Finally, as our observation, 1.0 mmol of **1a** in 2 mL of toluene, when treated with 2 mmol of TBHP could produce best results for this oxidative C-C cleavage reaction (entry 6).

Table 2. Scope of the oxidative C-C cleavage of HOP to acid[a]



entry	Reactent	Product	Yield (%) of 2
A B C D		 **2a**	R_1 - methyl - 92% ethyl - 90% i-propyl - 85% benzyl - 85%
E F G		 **2b**	R_1 - methyl - 95% ethyl - 89% benzyl - 85%
H I		 **2c**	R_1- methyl - 82% ethyl - 81%
J K		 **2d**	R_1- methyl - 90% benzyl - 75%
L		 **2e**	82%
M N		 **2f**	R_1- methyl - 85% ethyl - 74%
O P Q		 **2g**	R_1- methyl - 93% ethyl - 87% benzyl - 80%
R S		 **2h**	R_1- ethyl - 78% benzyl - 70%
T U		 **2i**	R_1- methyl - 85% benzyl - 74%
V W		 **2j**	R_1- methyl - 71% ethyl - 68%
X		 **2k**	75%
Y		 **2l**	72%
Z		 **2m**	87%
AA		 **2n**	92%
AB		 **2o**	83%

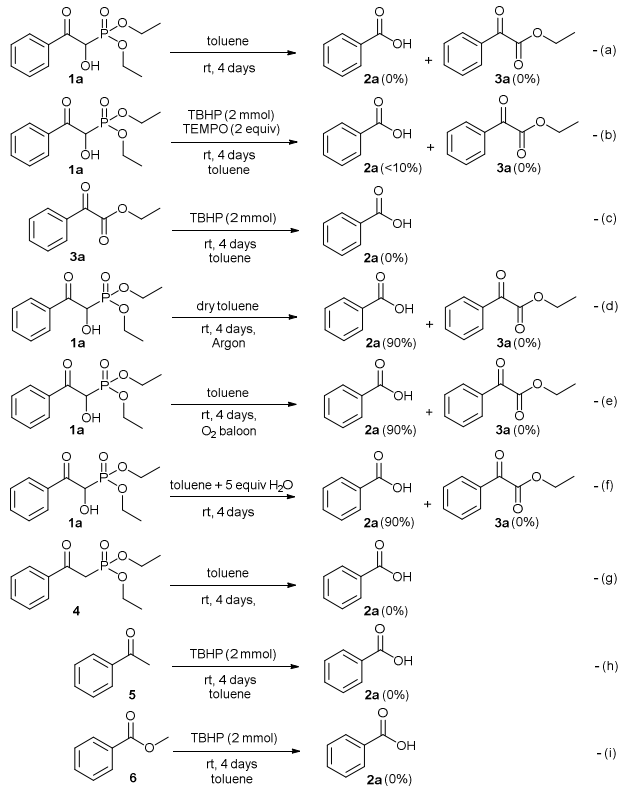
[a] Reaction conditions: HOP **1** (1.0 mmol), TBHP (2.0 mmol) and toluene (2 mL) at rt for 4 days.

With the optimized procedure in hand, we performed a series of experiments (A-AB) to verify the substrate scope of the reaction in terms of substitutions at aryl and phosphoryl groups of HOP **1**. As we observed, all these transformations were quite appreciable and obtained good to excellent yields. Irrespective of the substitution at aryl group of HOP, all these reactions could be smoothly converted to the required acids **2**. But various substitutions in phosphoryl group of HOP had brought significant changes in the yield of reaction. In general, we noticed bulkiness of phosphoryl group afforded lower yields of product **2**, for example methylated HOP's produced (reactions A, E, H, J, L, M, O, T, V, X and Y) higher yields than the ethylated substrates (reactions B, F, I, N, P, R and W). The same pattern was observed as a sequence in remaining HOP substrates, viz., iso-propylated (reaction C) and benzylated (reactions D, H, L, P, R and V) HOP's. Along with mono substituted HOP's, disubstituted HOP's also successfully underwent oxdative C-C cleavages to their corresponding acids (**2j**, **2k** and **2l**). Along with these results, we successfully conducted the reaction with thiophene, benzofuran based HOP's as well and isolated respective acids in good yields (92% for **2n** and 83% for **2o**).

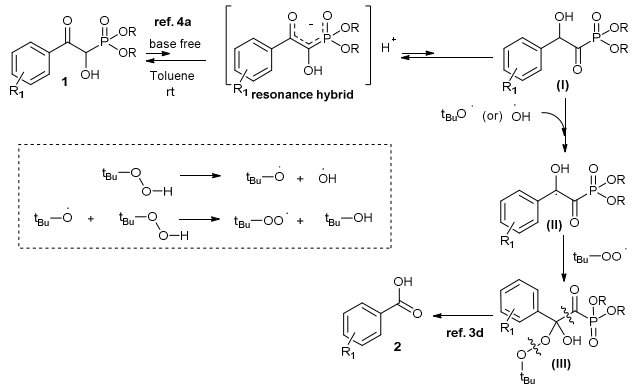
To interpret the reaction mechanism, we conducted few controlled experiments (Scheme 2). In the experiment (a), HOP **1a** on stirring in toluene at room temperature failed to produce **2a** and/ **3a**. This clearly indicates that room temperature is neither favourable for self catalyzed aerobic intermolecular nucleophilic displacement reaction to 2-oxoesters nor promotes oxidative hydroxylation to acids. Further to prove the nature of reaction in presence of TBHP, a reaction (b) was conducted between **1a** (1.0 mmol) and TBHP (2.0 mmol) with TEMPO (2.0 mmol) in **2** mL of toluene at room temperature for 4 days. In this case we isolated trace amounts of benzoicacid **2a**. This obviously indicates the free radical nature of the reaction. Experiment (c) indicated non participation of α-oxoester **3a** towards the generation of corresponding acid **2a**. In addition, generation of comparable yields in experiments (d), (e) and (f) highlighted the non participation of air (oxygen)/ water in our reaction. Finally, experiments (g), (h) and (i), wherein we failed to isolate expected products (**2a**) with β-ketophosphonate **4**, acetophenone **5**, and methylbenzoate **6** respectively as substrates, indicated the structural requirement of the *α-hydroxy-β-oxophosphoryl* group to this reaction.

On the basis of controlled experiments and literature reports,[3d,4a] a plausible reaction pathway for oxidative hydroxylation of HOP is described in Scheme 3. HOP **1**, as described before has a tendency to exist in different resonance structures. Under TBHP environment, isomer **(I)** as expected reacts with radicals ($OH^{\cdot}$, $tBuO^{\cdot}$) to produce a intermediate **(II)**

that ultimately on reaction with tertiarybutyl peroxy radical generates **2**.



Scheme 2. Controlled experiments.



Scheme 3. The plausible reaction mechanism for oxidative C-C cleavage of HOP.

In summary, we have established a metal-free oxidative C(CO)-C cleavage in *α*-hydroxy-*β*-oxo phosphonates (HOP). Notably, C-C cleavages on molecules bearing such linkages have never been reported before. Furthermore, such cleavages were successful in good yields with broad range of substrate scope. This protocol, certainly can find applications of HOP as synthons for generation of different valuable structures in future.

Acknowledgement

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