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One-pot and highly regio-selective 1, 3-dipole cycloaddition of azomethine ylide generated in situ to tetraethyl vinylidenebisphosphonate (VBP) catalyzed by cerium(IV) oxide

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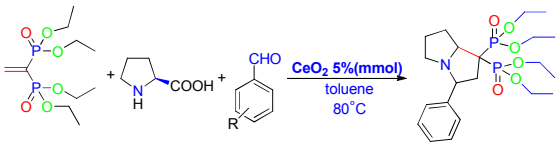
VBP reacts smoothly with L-proline and benzaldehyde derivates at 80°C in toluene catalyzed by Cerium (IV) oxide (CeO_2) to give the corresponding heterocyclic bisphosphonates in moderate yields (30-70%). Higly regio-selectivity of the 1, 3-dipole cycloaddition was observed. The structures of the targeted molecules are characterized by NMR (such as COSY, HSQC, and HMBC), IR and MS.



As one of the most powerful strategies for the synthesis of various five-membered heterocycles, the 1,3-dipole cycloaddition reaction has achieved great development and application in organic synthesis. However, most of these reactions are foucused on the reactive dienophile or dipolarophile[1] such as α, β-unsaturated carbonyl compounds and nitriles whose hindrance is small due to their structures are plane; that is to say, it is still a challenge to use the inactive or large hindrance dienophile or dipolarophile in the 1,3-dipole cycloaddition reaction. So we intend to employ VBP (Figure 1) having scarce reactivity (for example large hindrance due to the large tetrahedral structure of 'P')[2] to synthesize *gem*-bisphosphonates containing heterocycle, because heterocyclic *gem*-bisphosphonates are very likely to offer potent therapeutic opportunities for further success in several human pathologies[3], such as osteoporosis[4], cancer-related hypercalcemia[5], rheumatoid arthritis[6], and powerful anti-inflammatory drugs[7].

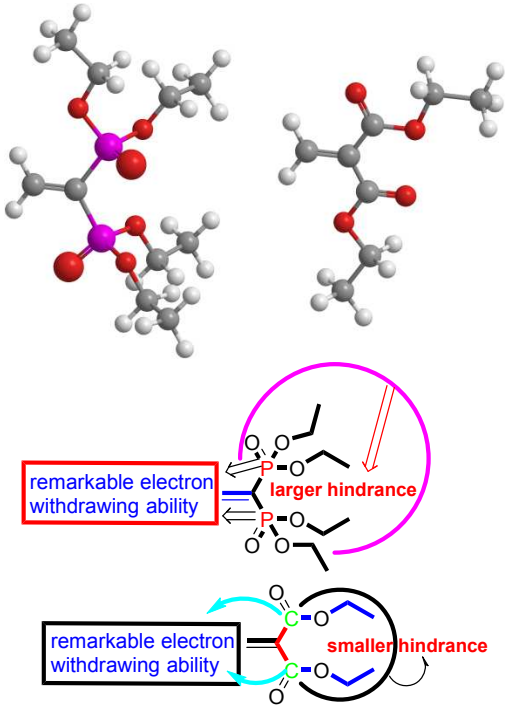


Figure 1 the Structure of VBP and Methylene diethylmalonate

To the best of our knowledge, although the electron-withdrawing ability of phosphonate groups is remarkable, there are only two examples of obtaining cyclic bisphosphonates using VBP via cycloaddition or Diels-Alder reaction but under hard conditions. Ye et.al used the cycloaddition of active nitrile oxides to VBP to get 4,5-dihydroisoxazoles containing phosphonyl group, which reacts 36h at most.[8] Renzo Ruzziconi et.al[9] employed

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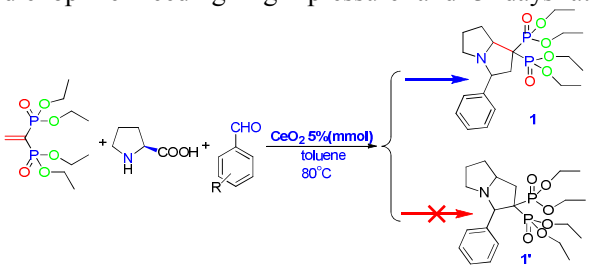
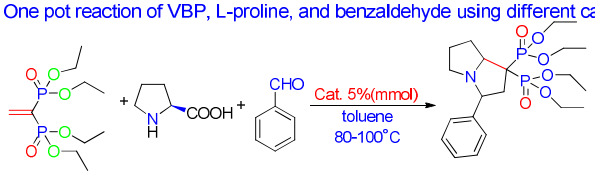
Diels-Alder reactions of 1,3-dienes using VBP as a dienophile needing high pressure and 3 days at most.



Scheme 1. Reaction of VBP with L-proline and aldehydes in toluene catalyzed by CeO_2

The importance of heterocyclic bisphosphonates as valuable blocks in the synthesis of biologically active molecules and the lack of information about these kinds of procedures encouraged us to research the one pot reaction of VBP with L-proline and a variety of aldehydes under milde conditions. Here, we report the results of this research(Scheme1).

Table 1
One pot reaction of VBP, L-proline, and benzaldehyde using different catalysts.



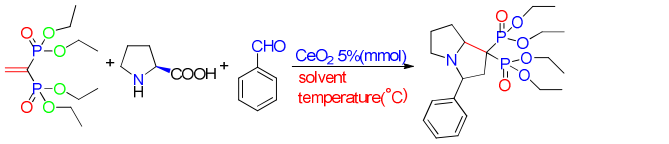
Entry	Catalyst	Base	Time(h)	Yield (%)
1	-	-	48	0
2	I_2	K_2CO_3	48	0
3	ZnO	-	48	0
4	ZnO	K_2CO_3	48	0
5	$ZnCl_2$	-	48	0
6	CuI	-	48	0
7	CuO	-	48	0
8	$FeCl_3$	-	48	0
9	CuBr	-	48	0
10	$CeCl_3{\cdot}7H_2O$	-	48	0
11	$InCl_3$	-	48	0
12	CuCl	-	48	0
13	-	K_2CO_3	48	0
14	-	Et_3N	48	0
15	$(CF_3SO_3)_3Yb$		48	0
16	MgO(nano)		5	50
17	Yb_2O_3		5	60
18	CeO_2		5	68
19	Sm_2O_3		5	30

The choice of an appropriate reaction solvent and catalyst is much of importance for successful synthesis. At the beginning, inspired by Babak Kaboudin and Tsutomu Yokomatsu[10], we chose the reaction of VBP(1mmol) with L-proline (1.5mmol) and benzaldehyde (1.2mmol) in toluene under catalyst-free condition as a model reaction trying every order of the addition of starting materials, but in vain (Table 1 entry 1).

However, we still believed that this transformation can proceed smoothly if we choose proper catalysts. Encouraged by Habib Firouzabadi and Nasser Iranpoor[11], after screening a series of catalysts, we found MgO, CeO_2 ,Yb_2O_3 and Sm_2O_3 are the proper candidates (Table 1 entries 16-18). So we chose CeO_2 as the best catalyst to optimize the model reaction.

With the best promotor in hand, we also studied the solvent effect. We tried a variety of solvents. Our studies suggested that toluene was the ideal solvent for this reaction (Table 2). The reaction in other solvents such as DMF and MeOH nearly did not proceed (Table 2 entries 1-5). The reaction at 50, 70, and 80°C can proceed smoothly and provid the target product **1** in 35%, 62%, and 68% (Table 2 entries 6-8)isolated yields within 12 h, 8 hour, and 5h, respectively, but cannot get the target molecular in 100 and 110°C (Table 2 entries 9-10).

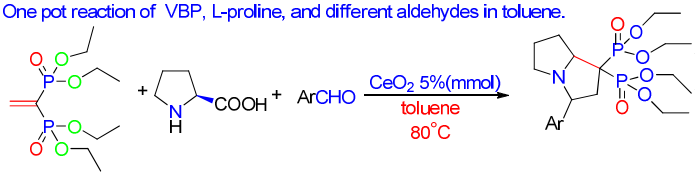
Table 2
One pot reaction of VBP, L-proline, and benzaldehyde in different solvent systems.

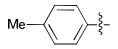
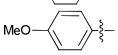
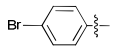
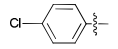
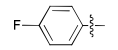
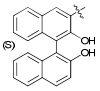
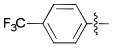


Entry	Solvent	Temp(°C)	Time(h)	Yield (%)
1	THF	66	48	trace
2	MeOH	65	48	trace
3	Xylene	80	48	trace
4	EtOH	78	48	trace
5	DMF	80	48	trace
6	toluene	50	12	35
7	toluene	70	8	62
8	toluene	80	5	68
9	toluene	100	5	trace
10	toluene	110	5	trace

After getting the optimized conditions, a range of aromatic aldehydes can react smoothly with L-proline and VBP, except the aliphatic aldehydes (Table 3). The structure of products such as **1** are identified by spectroscopic analysis[12] (^{1}H, COSY, ^{13}C NMR, HSQC, HMBC and ROESY) (Figure 2).Considering the reaction a 1,3-dipolar cycloaddition, the remarkable electron-withdrawing ability of the two phosphonate groups should contribute to decrease the LUMO energy of the dipolarophile (VBP), and meanwhile the coefficient at the

Table 3
One pot reaction of VBP, L-proline, and different aldehydes in toluene.



Compound (Entry)	Ar	Time(h)	Yield (%)
1		5	68
2		5	70
3		5	55
4		5	45
5		5	20
6		5	40
7		5	60
8		5	30
9		5	55

unsubstituted carbon increases. In the same time the presence of the phenyl group at one terminal carbon of the dipole make both the HOMO energy and the coefficient at the benzylic carbon to increase. Therefore, according to the frontier orbital theory the regioselectivity of the reported reaction is correct and reasonable. So the relatively high $^{3}J_{P\text{-}C}$ value (10.1 Hz) between the benzylic carbon at 68.45ppm (P-C-C-CH, see ESI) and the two *gem*-phosphorous, compared with the low value of the $^{2}J_{P\text{-}C}$ between the tertiary carbon at 69.43ppm, apparently a singlet, and the two *gem*- phosphorous would had been sufficient. Based on the ^{31}P NMR , for normal aromatic aldehydes as starting materials, there are two peaks (24.5ppm–25.9ppm) except **8** (23.67ppm) which indicates that the final products probably contain mixture of the four isomers as shown in figure 3. And for compound **8**, it is more likely that the bulky binaphthol backbone make the enantiomer **8**a and **8**a′ as the main product (Figure 4).

As depicted in Scheme 2, a possible reaction cycle for aromatic aldehydes is proposed. The iminium cation **I** is reversibly produced after the condensation of L-proline with benzaldehyde, then oxazolidinone **II** is reversibly formed for electron-rich aromatic aldehydes; but for the electrondeficient aromatic aldehydes such as *p*-chlorobenzaldehyde, the iminium specie **I** may directly undergo decarboxylation to form the azomethine ylide of which **III**, **IV**, **V** and **VI** are the resonance structure[13].

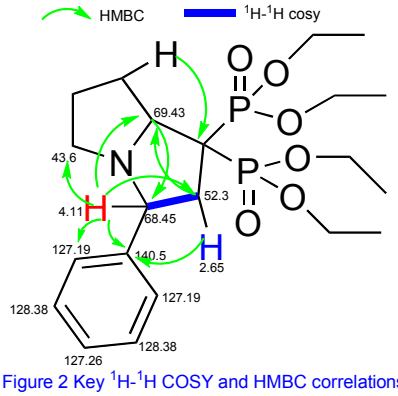


Figure 2 Key ^{1}H-^{1}H COSY and HMBC correlations of **1**

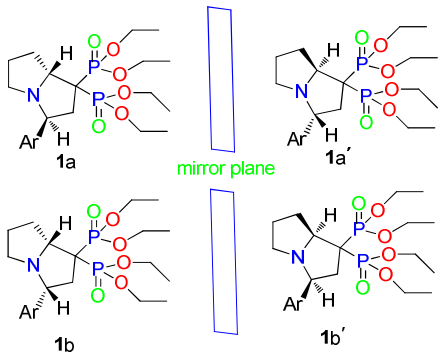


Figure 3

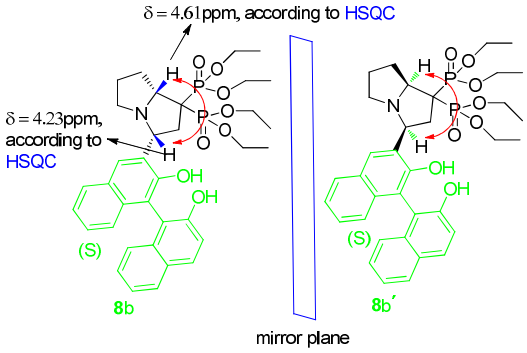
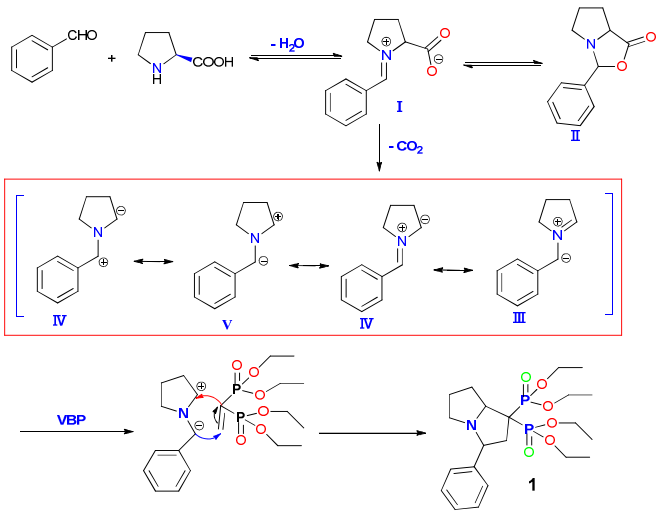


Figure 4 ROESY of **8**

V then react with VBP to form the stable targeted product **1**.That azomethine ylide is nonstable and its producing rate for electrondeficient aromatic aldehydes is faster than those of electron-rich aromatic aldehydes leads to some of them cannot fully react with VBP before they decompose, and thus rationalize that yields of desired products are higher for electron-rich aromatic aldehydes. Aromatic aldehydes with active hydrogen also cannot undergo further reaction or at a very low yield (Table 3 entry 8),

because the active hydrogen may decompose the azomethine ylide which is immune to proton. Besides that, we also found that *o*-substituted aromatic aldehydes can hardly carry on the reaction due to the neighbouring hindrance effect.



Scheme 2

In conclusion, VBP reacts smoothly with L-proline and benzaldehyde derivates at 80°C in toluene catalyzed by Cerium (IV) oxide (CeO_2) to give the corresponding heterocyclic bisphosphonates in moderate yields (30-70%). The structures of the targeted molecules are characterized by NMR (such as COSY, HSQC, and HMBC), IR and MS. The isomers can be found according the ^{31}P NMR, but it's difficult for us to isolate them one by one through column chromatography on silica gel because of few differences of the Rf values among isomers.

However, the readily method, mild reaction conditions, and moderate to good yields should make this strategy an efficient and a useful contribution to the synthesis methodologies of heterocyclic bisphosphonates.

Acknowledgment

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