Tetrahedron Letters 59 (2018) 1038–1041

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Practical way for the synthesis of 3,3′-bis-substituted benzo[*d*][1,2] oxaphosphole 2-oxides by phosphonylation of in situ generated *o*-quinone methides

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ARTICLE INFO

Article history:
Received 28 December 2017
Revised 26 January 2018
Accepted 29 January 2018
Available online 31 January 2018

Keywords:
Benzo[*d*][1,2]oxaphosphole 2-oxide
Orthoquinone methide
Michael addition reaction
Phosphonylation
Phosphoric acid

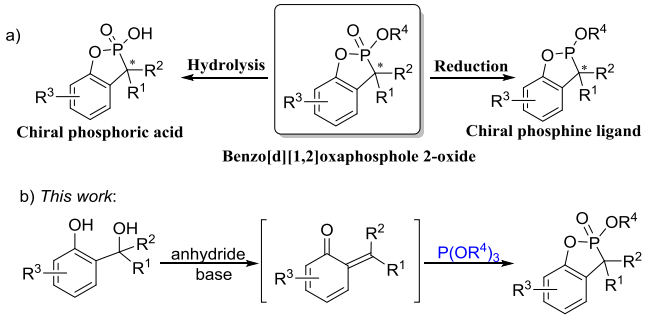
ABSTRACT

Phosphonylation of the pretreated 2-(hydroxymethyl)phenol derivatives with acetic anhydride using trialkylphosphites as the nucleophilic reagents was reported, providing a practical way to the synthesis of novel highly steric 3,3′-bis-substituted benzo[*d*][1,2]oxaphosphole 2-oxides.

Introduction

Benzo[*d*][1,2]oxaphosphole 2-oxides are a type of cyclic organophosphorus compounds, which are used as precursors of stabilized carbon-centered radicals,[1] photoluminescent complexes,[2] extractants,[3] as well as the intermediates to the synthesis of phosphoric acid catalysts[4] and the ligands for metal catlysis.[5] Especially, if benzo[*d*][1,2]oxaphosphole 2-oxide derivatives have a rigid chiral carbon center at the 3-site of benzo[*d*][1,2]oxaphosphole ring, just like the chiral oxazoline coordinating group which have played a significant role in the advancement of transition metal-based asymmetric catalysis,[6] they could be potentially versatile precursors for the development of chiral phosphoric acid catalysts and phosphine ligands (Scheme 1a).

Given their high importance, there is ongoing interest in the development of convenient and general protocols for the synthesis of benzo[*d*][1,2]oxaphosphole 2-oxides. Julia Pérez-Prieto and co-workers respectively reported the synthesis of 3-mono-substituted benzo[*d*][1,2]oxaphosphole 2-oxides via the reaction of hydroxyalkylphenols **2** with PBr_3/HBr and then with phosphite[1c] or the reaction of hydroxyalkylphenols with triethyl phosphite.[7] Phil Ho



Scheme 1. Synthesis of 3,3′-bis-substituted benzo[*d*][1,2] oxaphosphole 2-oxide and its potential application.

Lee and co-workers reported an efficient synthetic method of benzoxaphosphole 1- and 2-oxides through a Pd-catalyzed C(sp^2 and sp^3)-H activation/C—O bond formationunder aerobic conditions.[8] However, the synthetic strategies to the synthesis of 3,3′-bis-substituted benzo[*d*][1,2]oxaphosphole 2-oxides with highly steric hindrance received less attention. Orthoquinone methides (*o*-QMs) generated in situ from 2-(hydroxymethyl)phenols have received much attention in organic synthesis due to their rich synthetic transformations such as Michael addition reaction with

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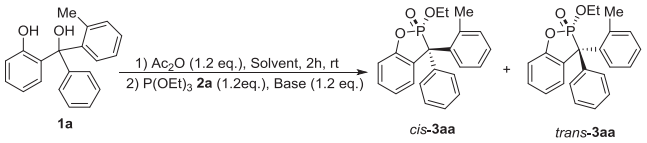
https://doi.org/10.1016/j.tetlet.2018.01.093
0040-4039/

Table 1
Optimizations of the conditions.[a]



Entry	Solvent	T (°C)	Base	Yield (%) of *cis*-**3aa**[b]	Yield (%) of *trans*-**3aa**[b]	Total yield (%) of **3aa**	*dr*[c]
1	CH_2Cl_2	rt	No	17	64	81	1:3.72
2[d]	CH_2Cl_2	rt	NEt_3	20	33	53	1:1.81
3[e]	CH_2Cl_2	rt	No	20	47	67	1:2.35
4	THF	rt	No	20	58	78	1:2.91
5	PhMe	rt	No	21	44	65	1:2.18
6	CH_3CN	rt	No	18	56	74	1:3.11
7	$(Et)_2O$	rt	No	9	25	34	1:2.71
8	DMF	rt	No	Trace	Trace	Trace	
9	CH_2Cl_2	rt	Thiourea	14	56	70	1:4.08
10	**CH_2Cl_2**	**rt**	**NEt_3**	**11**	**74**	**85**	**1:6.75**
11	CH_2Cl_2	rt	DMAP	27	61	88	1:1.87
12	CH_2Cl_2	rt	DABCO	22	50	72	1:1.25
13	CH_2Cl_2	rt	$EtN(i\text{-}Pr)_2$	13	45	58	1:3.42
14	CH_2Cl_2	20	NEt_3	9	56	65	1:6.82
15	CH_2Cl_2	10	NEt_3	5	33	38	1:6.91
16[f]	CH_2Cl_2	0	NEt_3	3	16	19	1:7.01
17[g]	CH_2Cl_2	−10	NEt_3	Trace	7	7	1:7.08
18[g]	CH_2Cl_2	−20	NEt_3	–	–	–	–

[a] **1a** (0.4 mmol) and Ac_2O (0.48 mmol, 1.2 eq.) were stirred in solvent (2 mL) for 2 h at room temperature, then $P(OEt)_3$ (0.48 mmol, 1.2 eq.) and base (0.4 mmol, 1 eq.) were added and further stirred for 12 h.
[b] Isolated yield.
[c] The *dr*-value was monitored by crude ^1H NMR.
[d] AcCl (0.5 mmol, 1.2 eq.) instead of Ac_2O was used.
[e] Boc_2O (0.5 mmol, 1.2 eq.) instead of Ac_2O was used.
[f] Reaction for 12 h.
[g] Reaction for 36 h.

carbon, nitrogen,[9] sulfur, and oxygen nucleophiles.[10] We envisioned that trialkylphosphite used as nucleophile could react with acylated 2-(hydroxy(aryl)methyl)phenol,[11] a good type of *o*-quinone methides precursors,[12] to give the Michael addition product which was further converted to benzo[*d*][1,2]oxaphosphole 2-oxide *via* subsequent cyclization and the transformation of P(III) to P(V) (Scheme 1b).[13] Comparing with the recent report of phosphorodiamidic acids catalyzed phosphonylation of in situ formed *o*-quinone methides to generate uncyclized diaryl phosphonates,[14] herein, we wish to report the synthesis of 3,3′-bis-substituted benzo[*d*][1,2]oxaphosphole 2-oxides from 2-(hydroxymethyl) phenols.

Results and discussion

At the beginning of our studies upon this phosphonylation process, reactions of 2-(hydroxy(phenyl)(*o*-tolyl)methyl)phenol (**1a**) with $P(OEt)_3$ (**2a**) were investigated as our model reaction under different conditions (Table 1). We are glad to see that when the mixture of starting materials **1a** and Ac_2O stirred in CH_2Cl_2 for 2 h at room temperature were further treated with **2a** at room temperature for 12 h, the desired 2-ethoxy-3-phenyl-3-(*o*-tolyl)-3*H*-benzo[*d*][1,2]oxaphosphole 2-oxide (**3aa**) with *cis*- and *trans*-configurations were obtained in 17% and 64%, respectively (Table 1, entry1). The diastereoselectivity of *cis*-**3aa** to *trans*-**3aa** is 1:3.72, which was determined by crude ^1H NMR. However, in the reaction of 2-(hydroxymethyl)phenol **1a** with **2a**, early reported methods[1c,7] only gave trace of desired product **3aa**. Other acylation reagents such as AcCl (Table 1, entry 2) and $(Boc)_2$ (Table 1, entry 3) instead of Ac_2O were used, delivering the lower total yields of **3aa** with lower *dr*-values. From the screen of solvents (Table 1, entries 1 and 4–8), it was found that CH_2Cl_2 was the best solvent and using DMF as the solvent couldn't give the corresponding products. In order to improve the diastereoselectivity of this phosphonylation process, the addition of base such as organic and inorganic bases was investigated (Table 1, entries 10–13). As the base, the addition of NEt_3 (1 equiv.) could remarkably raise the diastereoselectivity, affording the **3aa** in 85% of total yield and 1:6.75 of the ratio of *cis*-**3aa** to *trans*-**3aa**. However, the stronger bases such as DMAP and DABCO than NEt_3 delivered lower diastereoselectivities. Moreover, thiourea often used as the activator to promote the transformation of α,β-unsaturated ketone was tested in this reaction,[15] and showed that the addition of thiourea could slightly improve the diastereoselectivity (Table 1, entry 9). Along with the decrease reaction temperature, the diastereoselectivity could slightly increase, but the total yield of **3aa** was remarkably reduced (Table 1, entries 14–17).

With this optimized result in hand, we explored the substrate scope of this phosphonylation process (Table 2). A series of 2-(hydroxymethyl)phenols (**1b**–**m**) with different substituents were tested. It is important to note that more steric phenols such as **1d** (Table 2, entry 3), **1f** (Table 2, entry 5) and **1j** (Table 2, entry 9) couldn't give the corresponding desired products **3**. Moreover, substrates **1k**–**m** containing a halogen substituent on the phenol ring only afford the acyclic Michael addition products **4ka**–**ma**, respectively (Table 2, entries 10–12). It is maybe due to the electron-withdrawing property of halogen-atom that led to the decrease of nucleophilicity of phenolic hydroxyl group, that can't promote the formation of benzo[*d*][1,2]oxaphosphole 2-oxides. Other trialkylphosphites such as **2b** and **2c** can also give the desired benzo[*d*][1,2]oxaphosphole 2-oxides in good yields (Table 2, entries 13 and 14).

Other 2-(hydroxymethyl)phenols **1o** and **1p** were also investigated in this phosphonylation process (Scheme 2). For **1o**, acylated