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Bromophosphoalkoxylation of olefins with organic phosphates, cyclic ethers and NBS

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ABSTRACT

A variety of structurally novel phosphoalkoxy ester derivatives were prepared via highly regio- and diastereoselective four-component reaction involving olefin, cyclic ether, halogen reagent and organic phosphate. All components can be varied flexibly and moderate to excellent yields were obtained at room temperature. Several of these ester derivatives showed strong anticancer activity against human lung adenocarcinoma cells.

1. Introduction

Phosphate esters are of great importance because of the ubiquity of phosphate-containing molecules in biological processes including signalling pathways, information storage and energy transfer.[1] An enormous variety of biomolecules are encountered in the form of phosphate esters such as nucleotides, proteins and some secondary metabolites.[2] As a result, these biodegradable and short-lived compounds have been a topic of interest for many years, with applications mainly directed towards the bioorganic and medicinal chemistries.[3] In terms of their modes of action, for example, these compounds are involved in the inhibition of acetylcholine esterase (AChE)[4] and thus have also found numerous applications in insecticides, fungicides, herbicides and pesticides.[5] Therefore, the development of new protocols with green procedure for the introduction of phosphate would be important, especially in the areas of drug discovery, organic synthesis, and material science.

Phosphorylation in biological systems is easily carried out by ATP-dependent enzymes including kinases and phosphatases,[6] however, synthetic procedures of phosphorylation are limited and generally involve some hectic and tedious operations, including extraction and purification. This leads to synthetic inefficiency as well as generates large amount of wastes.[7] Many of these reactions are generally performed by using hazardous and toxic inorganic salts.[8] This leads to limiting their applications in organic synthesis. In order to overcome these problems and find new bioactive phospho-compounds, we decided to investigate one-pot processes consisting of concatenations of elementary organic reactions under similar conditions.[9] The ring-opening reactions of cyclic ethers are effective approaches to produce difunctional active intermediates.[10] Among ethers, tetrahydrofuran (THF) has been extensively studied. It acts as an important 4-carbon building block for organic synthesis, polymer chemistry and medicinal chemistry.[11] Lewis and inorganic acids,[12] transition metals[13] and others[14] have been reported for THF ring opening reactions. However, to the best of our knowledge there are only few reports concerning the ring-opening reactions of cyclic ethers with phosphate allowing the formation of useful phosphorylated synthons for the synthesis of compounds of biological interest.[15]

Based on these preceding developments of the THF ring opening reactions, recently, we described the Brönsted acid catalyzed nucleophilic conjugate addition of cyclic ether to the α,β-unsaturated carbonyl compounds, in which the enolate intermediate was detained by halogen reagent and finally the heterolytic ring cleavage of oxonium cation produced α-bromo-β-alkoxylated carbonyl derivatives (Scheme 1A).[11c,d]

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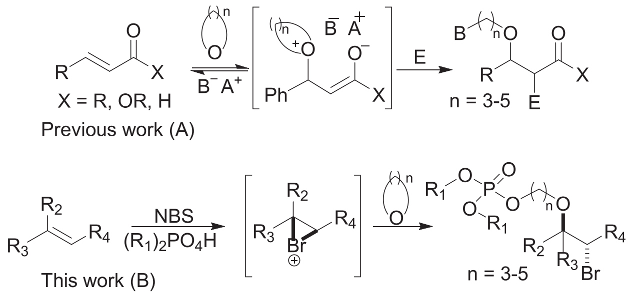


Scheme 1. Electrophilic four-component paradigm.

Seeking for further extension of these results, herein, we envisioned a straightforward method of phosphorylation, in which an olefinic double bond is triggered by halogen reagent and cyclic ether joined with the double bond in the presence of phosphate leading to the formation of halophosphoalkoxylated products (Scheme 1B). These highly functionalized compounds are otherwise difficult to prepare and find considerable attention for self-assembly spherical complexes and protein affinity tags.[16]

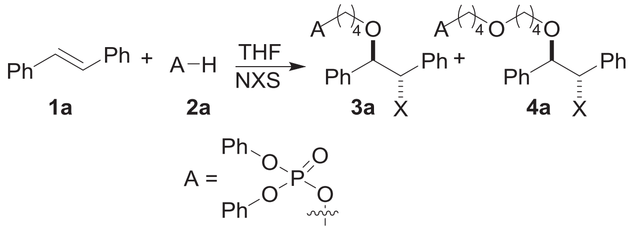
2. Results and discussions

Our study commenced with phosphoalkoxylation of stilbene **1a** with *N*-bromosuccinimide (NBS) as the halogen source in THF at room temperature. To our surprise, a 21% yield of THF dimerized product **4a** was obtained along with the formation of phosphoalkoxy product **3a** (Table 1, entry 1).[17]

Reaction conditions were further optimized to get the desired product **3a**. Other brominating reagents, including bromine, n-Bu_4NBr_3, 1,3-dibromo-5,5-dimethylhydantoin, $KBrO_3$/KBr were found relatively less effective.[17a] By employing less reactive *N*-chlorosuccinimide as a halogen reagent, the products were obtained in similar ratio, with lower yields (Table 1, entry 2). No desired products were observed, and may decompose, in case of *N*-iodosuccinimide (Table 1, entry 3). Disappointingly, both higher and lower temperatures were substandard (Table 1, entries 4–6). In contrast to our previous reports [11c,d], the addition of various Lewis acid catalysts including $GeBr_2$, $YbCl_3$, $CeCl_3$, etc. decreased the yields of both isomers.[17a] Further, investigation showed that the reaction yield and the ratio of products were highly dependent on the concentration, in which a higher reaction yield (51%) of **3a** was obtained under a diluted (33.3 mM) condition (Table 1, entry 7). Longer reaction time and two equivalents of NBS could improve the yield of **3a** to 69% and 73%, respectively (Table 1, entries 8, 9). The yield of **3a** was further improved by decreasing the equivalents of **2a** (Table 1, entry 10). Thus an appropriate acidic strength is important for optimal yield. Moreover, a mixed co-solvent of CH_2Cl_2 and THF produced almost the same yield (Table 1, entry 11).[17a] This observation is not in agreement to our previous results in which THF alone gave the best results; [11c,d] hence increase the applicability of this reaction to performs in different reaction media for other applications. Compared to our previous reports,[11c,d] the yields of isomers also did not change by changing the addition sequence of the reaction components.[17a] Over the years, phosphates have attracted special attention in natural and synthetic applications.[18] However, to the best of our knowledge, this is the first example which involves the THF ring opening and traps the corresponding intermediate for joining with alkene. More significantly, the resulting highly functionalized products are possible synthons which can be easily modified for the introduction of phosphate and different substituents at α-position for medicinally and biological privileged structures.[3,19] With the optimized reaction conditions in hand, we next tested the reaction scope by varying organic phosphates.

Aliphatic phosphates **2b** and **2c** worked well under these conditions, leading to the formation of phosphoalkoxylated products in good yields (Table 2, entries 1, 2). Besides, mixtures of diastereomers (dr=0%) were obtained with good to excellent yields in case of chiral **2d** and BINOL derived **2e** phosphates, respectively.[20]

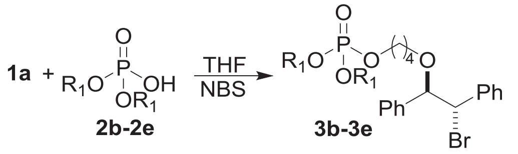
Table 1
Optimization of reaction conditions[a]

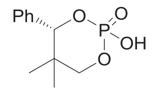
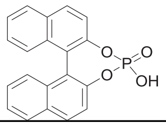


Entry	Temp (°C)	Halogen reagent	Yield (%)[b]	
			3a	**4a**
1	25	NBS	41	21
2	25	NCS	29	18
3	25	NIS	—	—
4	−78	NBS	—	—
5	0	NBS	14	4
6	65	NBS	12	Trace
7[c]	25	NBS	51	11
8[d]	25	NBS	69	15
9[e]	25	NBS	73	17
10[f]	25	NBS	79	11
11[g]	25	NBS	74	12

[a] **1a** (0.1 mmol), **2a** (0.15 mmol, 1.5 equiv), NBS (0.15 mmol, 1.15 equiv), were added in THF (1 mL) and stirred for 12 h at room temperature under argon.
[b] Isolated yield.
[c] THF (3 mL) was used.
[d] Reaction mixture was stirred for 24 h.
[e] NBS (2 equiv) was used.
[f] **2a** (1.01 equiv) was used.
[g] The reaction was stirred for 48 h in mixed co-solvent CH_2Cl_2 and THF.

Table 2
Phosphoalkoxylation of stilbene using various phosphates[a]



Entry	$(R_1)_2PO_4H$	Product	Yield (%)[b]
1	(*n*-Bu)$_2PO_4H$	**3b**	71
2	$(PhCH_2)_2PO_4H$	**3c**	76
3		**3d**	75
4		**3e**	83

[a] **1a** (0.1 mmol), acid (0.101 mmol, 1.01 equiv), NBS (0.2 mmol, 2.00 equiv), were added in THF (3 mL) and stirred for 24 h at room temperature under argon.
[b] Isolated yield.

We also investigated the substrate scope by testing different compounds containing the carbon-carbon double bond, including terminal olefins, cyclic olefins and allene (Table 3). Stereochemistry of the substrate, *cis*-stilbene, had little influence on the product yield (Table 2, entry 1).[20] The transformation maintained its

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