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Four-component α-bromo-β-phosphoalkoxylation of aromatic α,β-unsaturated carbonyl compounds†

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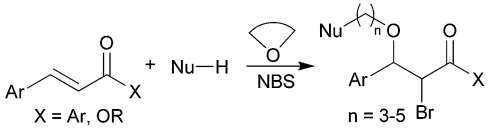
Novel α-bromo-β-phosphoalkoxylated carbonyl compounds were produced in moderate to excellent yields *via* highly selective four-component reaction involving NBS, a cyclic ether, an organic phosphate and an aromatic α,β-unsaturated carbonyl compound. A number of experimental observations suggested that the reaction is likely initiated by an acid mediated nucleophilic conjugate addition followed by electrophilic trapping the enol intermediate and subsequent ring-opening of the cyclic ether.

Organophosphate compounds have received much attention due to their ubiquity in biological systems.[1] Analogs of natural phosphates display different chemical and biological properties, and are of high interest to biology and medicine.[2] To enrich the phosphorus chemistry and find new bioactive compounds, we decided to investigate the synthesis of some novel α-bromo-β-phosphoalkoxylated carbonyl compounds[3] by multicomponent reactions (MCR). Despite the rich literature on ring-opening of epoxides, aziridines and cyclopropanes,[4] there were few reports concerning the ring-opening of cyclic ethers with phosphates.[5,6] In addition, these organophosphates were prepared in aqueous solution and by using inorganic phosphates,[7] thus preventing the methods from a broad application in organic synthesis. Albeit phosphates have been widely used as Brønsted acid organocatalysts and it is less recognized that phosphates act also as nucleophilic reagent for the ring-opening of cyclic ether.

Herein, we describe a new reaction that involves four components, namely, *N*-bromosuccinimide (NBS), cyclic ether, α,β-unsaturated aromatic carbonyl compound and organic acid. This reaction leads to efficient formation of anti-α-bromo-β-alkoxyl phosphate derivatives (Scheme 1).

The idea behind this transformation was to utilize the activation capacity of Brønsted acid,[8] the nucleophilic nature of THF[9] and the potential of NBS-mediated electrophilic enol trapping.[10] In addition, the formation of highly destabilized oxonium cation of cyclic ether also triggered its heterolytic ring cleavage in this transformation.[11] To test the activation capacity of Brønsted acid, the cascade reaction was examined by screening different acids using chalcone[12] **1a** as the model substrate in the presence of NBS as a nucleophilic capturer and THF as a solvent (Table 1).

It was found that TfOH, CH_3CO_2H, $PhCO_2H$, phenol and 4-NO_2 were unable to catalyze this reaction (Table 1, entries 1–5). A few organic phosphates were tested and only the BINOL derived phosphate **3a** gave a moderate yield (Table 1, entry 6). These results showed that it was essential to tune the reaction conditions as well as acidic strength for acid mediated reactions.[14] Further, we tried to optimize the reaction. Interestingly, low yields were observed at either lower or higher temperatures (Table 1, entries 7–9). Other halogen reagents including bromine, *n*-Bu_4NBr_3, 1,3-dibromo-5,5-dimethylhydantoin, $KBrO_3$/KBr, *N*-iodosuccinimide (NIS), *N*-chlorosuccinimide (NCS) *etc.*, were also tested and relatively low yields were observed.[13] Water increased the solubility of **3a** but decreased the yield along with the formation of halohydrins (Table 1, entry 10).[15] Reaction was also tested in solvent mixtures. Although chlorinated solvents were effective for this reaction, THF alone gave the best results.[16] Interestingly, when **3a** was divided into four aliquots and added one aliquot after every 5 h, the yield dropped dramatically (Table 1, entry 11), while similar procedures with NBS increased the yield significantly (Table 1, entry 12).



Scheme 1 General acid mediated four components reaction.

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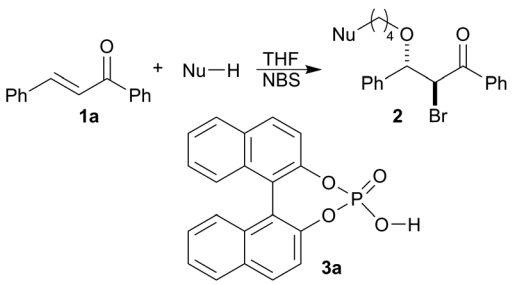
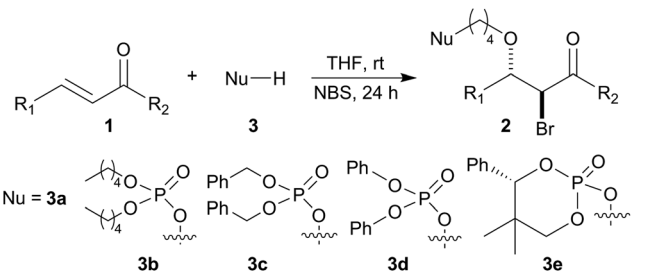
Table 1 Optimization of reaction conditions[a]



Entry	Nu–H	Temp. (°C)	Yield[b] (%)
1	TfOH	25	—
2	CH_3CO_2H	25	—
3	$PhCO_2H$	25	—
4	Phenol	25	—
5	4-NO_2-Phenol	25	—
6	**3a**	25	59
7	**3a**	−78	Trace
8	**3a**	0	23
9	**3a**	65	24
10[c]	**3a**	25	36
11[d]	**3a**	25	10
12[e]	**3a**	25	82

[a] Chalcone (0.2 mmol), acid (0.21 mmol, 1.01 equiv.), NBS (0.4 mmol, 2 equiv.), were added in THF (2 mL) and stirred for 24 h at room temperature under argon. [b] Isolate yield. [c] 10 mol% H_2O was added. [d] **3a** (0.5 equiv.) was added after every 5 h. [e] NBS (0.5 equiv.) was added slowly as solution in THF (0.2 mL) after every 5 h.

Table 2 Phosphoalkoxylation of aromatic enones[a]



Entry	Nu–H	Prod.	R_1	R_2	Yield[b] (%)
1	**3b**	**2b**	C_6H_5	C_6H_5	58
2	**3c**	**2c**	C_6H_5	C_6H_5	62
3	**3d**	**2d**	C_6H_5	C_6H_5	70
4	(*R*)-**3e**	**2e**	C_6H_5	C_6H_5	61
5	**3a**	**2f**	4-$OMeC_6H_4$	C_6H_5	—
6	**3a**	**2g**	4-OHC_6H_4	C_6H_5	—
7	**3a**	**2h**	C_6H_5	4′-$OMeC_6H_4$	83
8	**3a**	**2i**	4-FC_6H_4	C_6H_5	65
9	**3a**	**2j**	4-ClC_6H_4	C_6H_5	81
10	**3a**	**2k**	4-BrC_6H_4	C_6H_5	86
11	**3a**	**2l**	C_6H_5	4′-ClC_6H_4	55
12	**3a**	**2m**	4-ClC_6H_4	4′-ClC_6H_4	65
13	**3a**	**2n**	4-$NO_2C_6H_4$	C_6H_5	NDP
14	**3a**	**2o**	4-$CH(CH_3)_2C_6H_4$	4′-$NO_2C_6H_4$	48
15	**3a**	**2p**	C_6H_5	4′-$CF_3C_6H_4$	59
16	**3a**	**2q**	C_6H_5	4′-$CH_3C_6H_4$	77

[a] Enones (0.2 mmol) and **3a** (0.21 mmol) were added and stirred in THF followed by slow addition of NBS (0.1 mmol, 0.5 equiv.) at room temperature after each five hours and stirred for 24 h under argon. [b] Isolate yields of all possible isomers.

Having identified suitable reaction conditions, various organic phosphates were subjected to investigation. Moderate yields were observed in case of di-butyl, di-benzyl and enantiopure (*R*)-**3e** phosphates (Table 2, entries 1, 2, 4), which may be partly attributed to lower acidity of these phosphates. The adduct **2d** was isolated in a higher yield (Table 2, entry 3), as the corresponding phosphate **3d** was a relatively stronger acid. These results are consistent with our hypothesis of carbonyl activation by Brønsted acid. Over the years, chiral phosphate catalysts have been widely applied in different solvents, but to the best of our knowledge, this is the first example in which it involved for the ring opening of THF.[17] More significantly, it led to an apparent conjugate addition products of an oxygen-centred nucleophilic specie to α,β-unsaturated carbonyl compounds.[18,19] The analytical data of all compounds by ^{1}H NMR, ^{13}C NMR, HSQC and HRMS confirmed the structure of these products. Profoundly, in ^{1}H NMR spectra, a coupling constant of around 9.8 Hz in all products between the protons at C-1 and C-2 position revealed a *trans* configuration.[13]

Under optimized conditions, various α,β-unsaturated chalcones[21] were also tested using **3a**[20] as the acid catalyst (Table 2, entries 5–16). In many cases, the corresponding α-bromo-β-phosphoalkoxyl carbonyl compounds were separated in moderate to excellent yields.

Interestingly, the reactivity pattern of the C=C functionality was drastically affected by the presence of different substituents on benzene rings and was more pronounced on the benzene ring directly conjugated with the C=C bound. Thus, no desired products were found when the substrate bearing electron donating groups, 4-OH or 4-OMe (Table 2, entries 5, 6), were employed. However, excellent yield was observed for the chalcone bearing an electron donating group 4′-OMe (Table 2, entry 7). In general, chalcones with an electron withdrawing halogen atom on either aromatic ring produced desired products. Chalcones with 4-substituted halogen gave excellent yields (Table 2, entries 8–10), while those with 4′-substituted halogen gave relatively lower yields (Table 2, entry 9 *vs.* entries 11, 12). The chalcone with strong electron withdrawing group, 4-NO_2, on benzene ring conjugated with the C=C bond was inactive (Table 2, entry 13).[22] However, moderate yields were obtained for those having electron withdrawing group 4′-NO_2, or 4′-CF_3 attached to the C=O bond linked benzene ring (Table 2, entries 14, 15). Moderate yield was also obtained for 4′-Me chalcone (Table 2, entry 16). Moreover, no conversion was observed in case of aliphatic, cyclic and α-substituted chalcones.

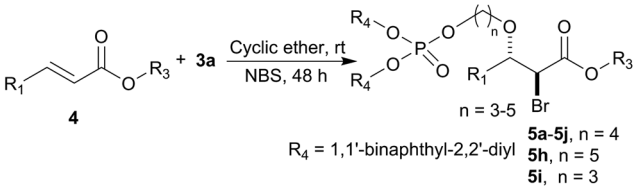
To further demonstrate the usefulness of this reaction, different α,β-unsaturated compounds were tested. Albeit no conversion of nitrostyrene, cinnamaldehyde and cinnamonitrile was observed, the yield was 72% in case of ethyl cinnamate

(Table 3, entry 1). Then, the scope of reaction was extended to various α,β-unsaturated esters (Table 3).

Except for those with electron-donating group (OH or NH_2) and highly electron withdrawing group 4-NO_2, other esters gave moderate to good yields. The 4-Br and 4-Cl esters produced desired products in excellent yields (Table 3, entries 2, 3). Further, the ester moiety was altered to study potential steric effects. The increased size of the ester moiety R_3 led to lower yields (Table 3, entries 1, 4–7). Interestingly, heterolytic ring cleavage was also observed when THF was replaced by tetrahydropyran or oxetane, and the corresponding products **5h** or **5i** were obtained in moderate yields (Table 3, entries 8 and 9).

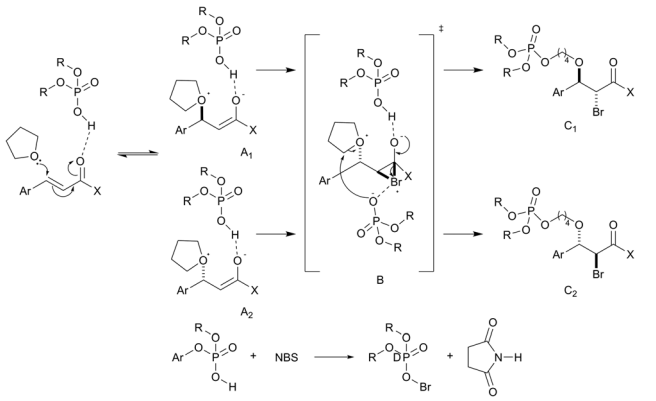
Further, a set of experiments were performed to illuminate the reaction mechanism.[13] First, the sodium salt of **3a** was prepared *in situ* and used in the model reaction but there was no product formation. Second, a higher yield was obtained when NBS was added slowly into a premixed solution of **1a** and **3a**, while the yield dropped when **3a** was added into a premixed solution of NBS and **1a**, supporting the idea of Brønsted acid activation and dearth of halonium cation (Table 1, entries 11, 12). Subsequently, the effect of chiral environment by chiral **3a** was investigated. Both *S*-**3a** and *R*-**3a** produced mixture of two diastereomers and no enantioinduction was observed,[13] suggesting that the reaction proceeded in a stepwise rather than concerted manor.[23] In ^{1}H NMR spectra, the coupling constant of 9.8 Hz between the protons at C-1 and C-2 position revealed a *trans* configuration. This assured high anti-diastereoselectivity around the double bond owing to an enol capturing at the opposite face of an oxonium cation.

Table 3 Phosphoalkoxylation of aromatic esters[a]



Entry	Prod.	R_1	R_3	Yield[b] (%)
1	**5a**	C_6H_5	CH_2CH_3	72
2	**5b**	4-BrC_6H_4	CH_2CH_3	75
3	**5c**	4-ClC_6H_4	CH_3	83
4	**5d**	C_6H_5	$CH(CH_3)_2$	63
5	**5e**	C_6H_5	$CH_2CH_2CH_3$	70
6	**5f**	C_6H_5	$CH_2C_6H_5$	69
7	**5g**	C_6H_5	CH_3	74
8[c]	**5h**	C_6H_5	CH_3	55
9[d]	**5i**	C_6H_5	CH_3	62

[a] Ester (0.2 mmol) and **3a** (0.21 mmol) were added and stirred in THF, followed by slow addition of NBS (0.1 mmol) as solution in THF (0.2 mL) at room temperature after each five hours and stirred for 48 h at room temperature under argon. [b] Isolate yields of all possible isomers. [c] Instead of THF, tetrahydropyran was used as a solvent. [d] Instead of THF, oxetane was used as a solvent. Note. d. r. was determined by chiral HPLC on CHIRALPAK IF column.



Scheme 2 Plausible reaction mechanism of α-bromo-β-phosphoalkoxylation of α,β-unsaturated compounds.

Thus, we favour a mechanistic pathway shown in Scheme 2. The reaction involves Brønsted acid activation of the carbonyl functionality, followed by a reversible nucleophilic conjugate addition of THF to the α,β-unsaturated carbonyl substrate leading to enolate intermediates A_1 and A_2. Subsequently, the electrophilic brominating source R_2PO_4Br (produced by the reaction of **3a** and NBS) captures the resulting nucleophilic enol and adds bromine to the double bond at the face exactly opposite to the oxonium cation. Finally, an intermolecular attack of the highly destabilized oxonium cation by phosphate anion results in the ring opening of THF and the formation of the phosphoalkoxlated product.[24]

It is noteworthy that the resulting highly functionalized compounds are important for self-assembly spherical complexes,[25] protein affinity tags,[26] and possible synthon which can be easily modified for the introduction of phosphate[27] and different substituents at α-position for medicinally and biological privileged structures.[7,28]

Conclusions

In conclusion, novel α-bromo-β-phosphoalkoxyl carbonyl compounds were produced in moderate to excellent yields *via* highly diastereo- and regioselective multicomponent reactions. The reaction is likely initiated by acid mediated nucleophilic conjugate addition followed by electrophilic trapping the enol intermediates. The strategy may be further developed as a new route for the challenging nucleophilic conjugate addition reaction. We are now extending this concept to the synthesis of other functionalized products and exploring potential applications for these compounds.

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