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Base-controlled reaction of α,β-unsaturated trifluoromethyl ketone and dialkyl phosphite

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ABSTRACT

Base-controlled selective reactions of α,β-unsaturated trifluoromethyl ketones with dialkyl phosphites were achieved. In the presence of DABCO, the Pudovik reaction took place readily to give the corresponding α-hydroxy phosphonates in high yields under mild conditions. While using DBU as base, the Phospha-Brook rearrangement of α-hydroxy phosphonates formed in the reaction occurred to afford phosphates as final products.

Organic phosphoric compounds are important targets for synthetic organic chemists.[1] α-Hydroxy phosphonate is an important structural unit in many biologically active compounds, such as pesticides, antibiotics, anticancer drugs, antiviral agents and enzyme inhibitors.[2] In recent years, many methods for the synthesis of α-hydroxy phosphonates have been developed *via* the α-hydroxylation of alkyl phosphonates,[3] the addition of trialkyl phosphites to aldehydes[4] or the reduction of keto phosphonates.[5] Besides these pathways, the addition of dialkyl phosphites to aldehydes, known as the Pudovik reaction,[2e,6] is undoubtedly the most straightforward and atom-economical one to α-hydroxy phosphonates. Normally, hydroxyphosphonates are the only isolated products in the Pudovik reaction of most aldehydes and ketones. However, in the case of carbonyl compounds containing anion stabilizing substituents at the α position[7] (e.g. α-dicarbonyl compounds, perfluoroalkyl aldehydes and ketones), phosphates were obtained as major products from the base-catalyzed Phospha-Brook rearrangement. For example, Zhu and coworkers have reported the synthesis of phosphates from fluorinated α,β-unsaturated phenylketones through the process of a DBU-catalyzed rearrangement.[8]

In continuation of our study on the application of α,β-unsaturated trifluoromethyl ketones,[9] we were also interested in exploring the phosphonylation of α,β-unsaturated trifluoromethyl ketones. Considering simple tertiary amines were much easier to handle than metallic reagents and might promote the reaction under mild conditions, the tertiary amine-catalyzed reactions of α,β-unsaturated trifluoromethyl ketones with diethyl phosphite were investigated and the control of reaction selectivity was achieved. The results are reported in this paper.

In our initial experiments, trifluoromethyl β-phenyl-α,β-unsaturated ketone[10] (**1a**) was treated with 2.0 equiv of diethyl phosphite in the presence of 0.5 equiv of quinine in diethyl ether at room temperature. Gratefully, the isomers of **2a** and **3a** were isolated in 86% overall yield with a ratio of 6:1 after 6 h (Scheme 1).

On the basis of literatures,[7,8] it is obvious that product **3a** was formed from **2a** as shown in Scheme 2. In the presence of base, α-hydroxy phosphonate **2a** produced through the Pudovik reaction of **1a** and diethyl phosphite could transform further to give anion **A**, which underwent Phospha-Brook rearrangement to give **3a** through anion intermediate **B**. The strong electron-withdrawing trifluoromethyl group could stabilize anion **B** and thus contribute to this transformation.

To get better selectivity, the reaction conditions were then scrutinized using the reaction of **1a** and diethyl phosphite as the model reaction. Firstly, various tertiary amines were tested and it was found that 95% of conversion and excellent selectivity for **2a** were obtained in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) at room temperature after 1.6 h (Table 1, entry 2, **2a**:**3a** > 95:5). Triethyl amine (Et_3N), *N*-methylmorpholine (NMM) and *N*,*N*-4-dimethylaminopyridine (DMAP) could also catalyze the reaction to give high region-selectivity, albeit the longer reaction time (6.5–68 h, entries 3–5). Pyridine known as a weak base could not promote this reaction well and only 5% of conversion was achieved

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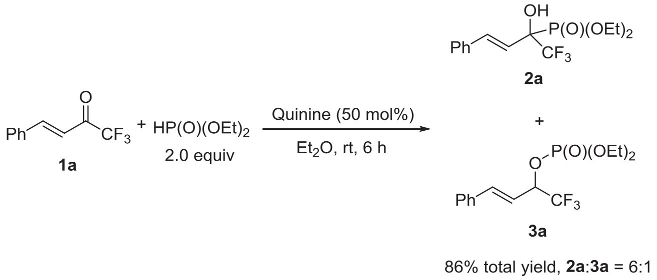
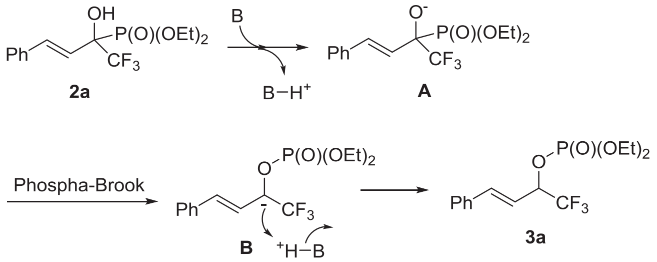


Scheme 1. The reaction of **1a** with diethyl phosphite in the presence of quinine.



Scheme 2. The mechanism for the formation of **3a** from **2a.**

after 3 days (entry 6). To our surprise, while using strong base 8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst, 100% conversion of **2a** was observed in only 5 min, and phosphate **3a** was obtained as major product with a ratio of **2a** and **3a** less than 5:95 (entry 7). This might be caused by the strong basicity of DBU (pKa = 12), which is much stronger than other bases tested[11] and could promote the Phospha-Brook rearrangement of **2a** easily to afford compound **3a**.

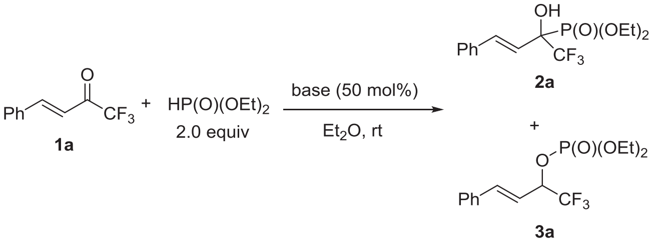
Various solvents were next screened to examine the feasibility of the reaction using DABCO as base. It was found that tetrahydrofuran (THF), toluene and dimethyl formamide (DMF) could not give better result although they also afforded **2a** as major product (Table 2, entries 2–4). Several undetermined products were formed in methanol (entry 5). Therefore, ethyl ether was chosen as solvent for the selective formation of α-hydroxy phosphonate. Further study showed that the catalyst loading of DABCO could be lowered down to 10 mol% without any erosion in yield and selectivity (entries 6–7). In the case of DBU-catalyzed reaction, full conversion and excellent selectivity were also achieved with 10 mol% of DBU in very short time (entries 8–10).

Under the optimized conditions, the scope of unsaturated ketones was investigated in the DABCO-catalyzed reaction. As shown in Table 3, aromatic unsaturated ketones **1**, regardless of electron-donating and electron-withdrawing substituents in the phenyl ring, could react with diethyl phosphite to give the corresponding products **2b**–**2d** in high yields with excellent selectivities (Table 3, entries 1–4). Ketones with naphthyl or furyl substituent also reacted well under the reaction conditions (entries 5–6). Furthermore, the reaction of diisopropyl phosphite with **1a** was also tested, and the desired product **2g** was obtained in 95% yield with a ratio of more than 95:5 (entry 7). Unfortunately, the reaction of aliphatic unsaturated ketone **1g** failed to give any expected products (entry 8).

Unsaturated ketones **1** were also evaluated in the DBU-catalyzed reaction and the results are summarized in Table 4. As expected, the reaction showed a wide scope for the structural variation of **1** and excellent regio-selectivity was achieved with phosphate **3** as major product in each reaction. High yields were obtained not only with phenyl substituted products **3a**–**3d** (Table 3, entries 1–4), but also with naphthyl and furyl-substituted products **3e**–**3f** (entries 5–6). Good result was also obtained when diisopropyl phosphite was used instead of diethyl phosphite (entry 7). Similarly, the reaction of aliphatic unsaturated ketone **1g** was unsuccessful (entry 8).

In summary, we have developed a base-catalyzed highly regioselective reaction of α,β-unsaturated trifluoromethyl ketones and dialkyl phosphites. Using DABCO as catalyst, the Pudovik reaction took place under mild conditions to give α-hydroxy phosphonate as major product. When DBU was used as catalyst, Phospha-Brook rearrangement of α-hydroxy phosphonate formed from the Pudovik reaction occurred further to afford the corresponding phosphate as final product in high yield. We believe that these fluorinated phosphoric compounds are useful structural motif

Table 1
The reaction of **1a** with diethyl phosphite in the presence of different bases.



Entry[a]	Base	pKa	Time (h)	Conv. (%)[b]	**2a**:**3a**[b]
1	Quinine	8.5	6	90	6:1
2	DABCO	8.7	1.6	95	>95:5
3	NEt_3	10.8	6.5	91	>95:5
4	DMAP	9.7	26	93	90:10
5	NMM	7.3	68	92	>95:5
6	Pyridine	5.2	71	5	–
7	DBU	12	5 min	100	<5:95

[a] Reaction conditions: **1a** (0.2 mmol), diethyl phosphite (0.4 mmol), base (0.1 mmol), Et_2O (2.0 mL), room temperature.
[b] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.