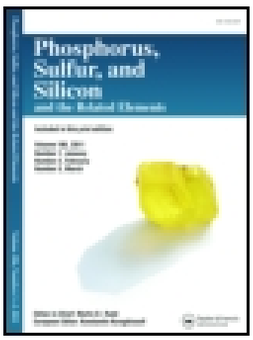

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Polystyrene-supported phosphine oxide-catalysed Beckmann rearrangement of ketoximes in 1,1,1,3,3,3-hexafluoro-2-propanol

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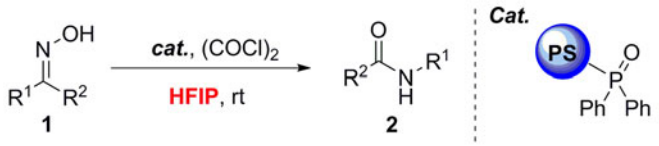
ABSTRACT

A polystyrene-supported phosphine oxide-catalysed Beckmann rearrangement of ketoximes in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) has been developed. Good substrate compatibility, mild reaction conditions, good yields as well as the reusability of the catalyst/solvent made this procedure more environmentally benign.

GRAPHICAL ABSTRACT



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KEYWORDS
Supported phosphine oxide; hexafluoroisopropanol; Beckmann rearrangement; ketoximes

1. Introduction

The Beckmann rearrangement is an important and useful reaction, which provides an atom-economic approach to construct amides and lactams from the corresponding oximes.[1–4] A very important application, through Beckmann rearrangement, in industry is the manufacture of ε-caprolactam, which is the precursor for the synthesis of the polyamide, nylon-6.[5] However, traditional Beckmann rearrangement requires the use of a strongly acidic catalyst and high temperature. Therefore, recent studies have focused on the development of suitable procedures by using various metal catalysts (Rh,[6] Ru,[7] Pd,[8] Zn[9] and calcium salts[10]), organocatalysts or promoters[11] (cyanuric chloride,[11a] bis(2-oxo-3-oxazolidinyl)-phosphinic chloride,[11b] triphosphazene,[11c] tosyl chloride,[11d] propylphosphonic anhydride,[11e] trifluoroacetic acid,[11f] dichloroimidazolidinedione,[11g] cyclopropenium salts,[11h] boronic acid,[11i] Mukaiyama Reagent,[11j] Vilsmeier reagent[11k] and hypervalent iodine[11l]), heterogeneous catalysts[12] as well as alternative reaction mediums (supercritical water[13] and ionic acid[14]). While acknowledging these contributions, there are still issues to be addressed in some instances. For example, most of the reported reactions were carried out under refluxing condition; some acid catalysts were toxic and corrosive;[11a,b,d,e,f] and additives were usually required to promote the reactions when organocatalysts were employed.[11b,d] Moreover, noble catalysts, supercritical water and ionic acids were expensive. Thus, the development of facile and efficient methods for the Beckmann rearrangement is still highly desirable.

Other approaches using activated triphenylphosphine moieties for Beckmann-like rearrangements have also been reported.[15] However, phosphine oxide was generated during the reaction.[15a,d] Recently, the application of catalytic phosphine oxide/oxalyl chloride combination in organic transformations has received much attention. The *in situ* generated $[ClPPh_3]^+Cl^-$ can efficiently promote the chlorination of alcohols and dehydration of amides (Scheme 1).[16–20] Inspired by these works, we envisioned that intermediate chlorophosphonium chloride **A** could react with a ketoxime via oxygen to give intermediate **B**, which then undergoes elimination to generate intermediate **C** (or the imidoyl chloride **D**) and phosphine oxide. The intermediate **C** may be attacked by water or proceed through a self-propagating pathway to afford the Beckmann rearrangement product. We also believed that utilization of a polymer-supported phosphine oxide catalyst could benefit the separation and purification process since the catalyst could be readily recovered by simple filtration. Moreover, the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent may favor the N-O bond cleavage of intermediate **B** and **E** via its high hydrogen bonding as well as good substrate solubility.[21–27] Herein, we wish to report a facile and efficient heterogeneous phosphine oxide-catalysed Beckmann rearrangement of ketoximes in HFIP (Scheme 1).

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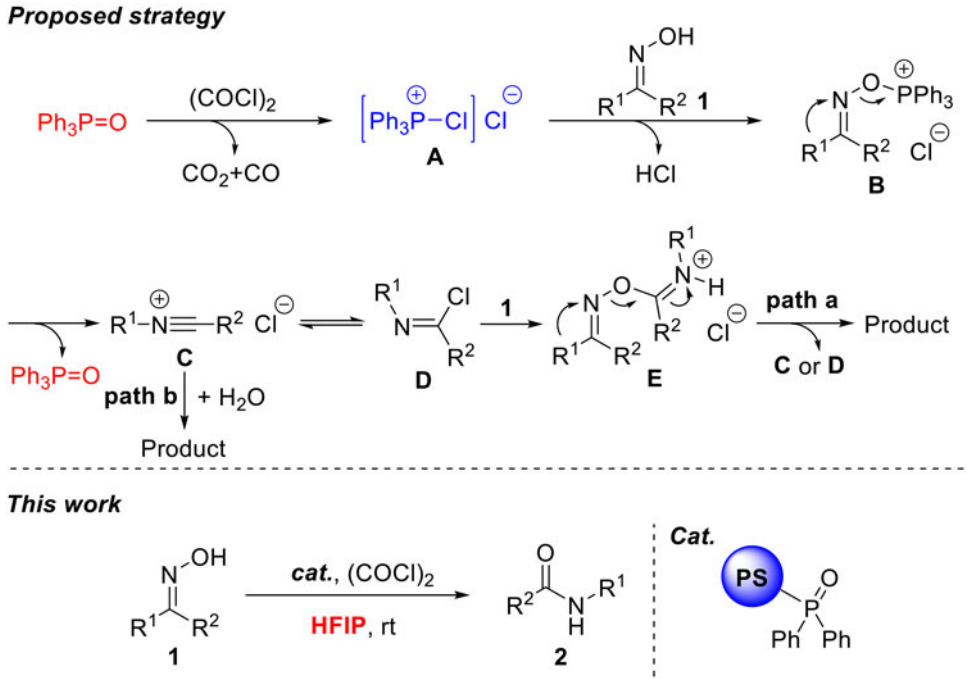
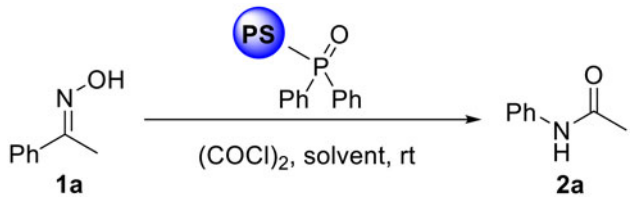


Scheme 1. Phosphine oxide-catalyzed the Beckmann rearrangement.

Table 1. Optimization of reaction conditions[a].



Entry	Catalyst (mol%)	$(COCl)_2$ (equiv)	Solvent	t (h)	Yield (%)[b]
1	10	1	CH_3CN	12	0
2	10	1	DMF	12	74
3	10	1	DMSO	12	30
4	10	1	dioxane	12	0
5	10	1	THF	12	0
6	10	1	toluene	12	0
7	10	1	H_2O	12	0
8	10	1	CF_3CH_2OH	2	84
9	10	1	HFIP	2	99
10	5	1	HFIP	2	99
11	2.5	1	HFIP	2	99
12	1	1	HFIP	6	72
13	–	1	HFIP	12	0
14	–	–	HFIP	2	11[c], 0[d]
15	2.5	1	HFIP	2	95[e]
16	2.5	1.5	HFIP	1.5	99
17	2.5	2	HFIP	1	99
18	2.5	–	HFIP	12	0

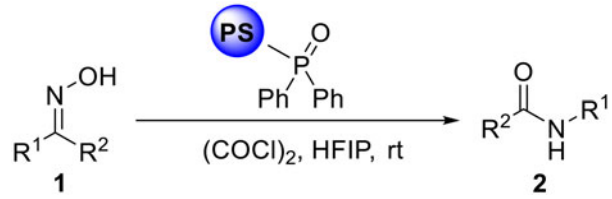
[a] Reaction conditions: **1a** (0.5 mmol), solvent (2 mL), catalyst (1.2–1.8 mmol/g, on polystyrene cross-linked with 2% divinylbenzene), $(COCl)_2$, room temperature. [b] Isolated Yields. [c] HCl (36–38 wt %, 2.5 mol%) was used as the catalyst. [d] DMF as the solvent. [e] Et_3N or Na_2CO_3 was added.

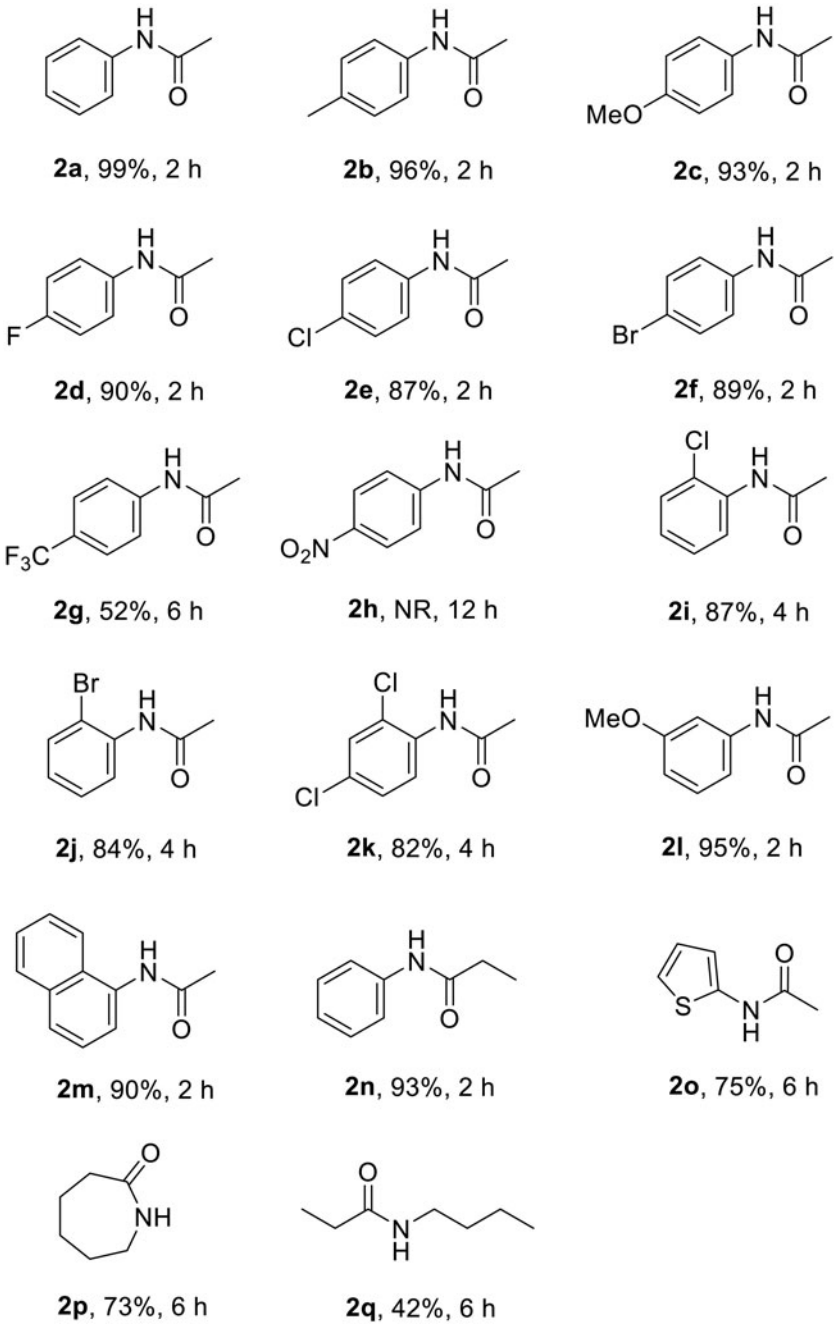
2. Results and discussion

To test the hypothesis, initially, ketoxime **1a** was selected as the model substrate to optimize the reaction conditions (Table 1). It was observed that when a mixture of **1a** (0.5 mmol), oxalyl chloride (1 equiv) and supported phosphine oxide (10 mol%) was stirred in acetonitrile (2 mL) at room temperature for 12 h, no desired product **2a** was detected (entry 1). Switching the solvents to DMF or DMSO provided **2a** in 74% and 30% yields, respectively (entry 2 and 3). However, reactions in other solvents such as dioxane, tetrahydrofuran, toluene and water led to the failure of the reaction (entries 4 – 7). Pleasingly, good to excellent yields were obtained within only 2 h when 2,2,2-trifluoroethanol or HFIP was used as the solvent (entry 8 and 9). It was assumed that 2,2,2-trifluoroethanol and HFIP not only showed good substrate solubility but might favor the N-O bond cleavage of intermediate **B** and **E** via its high hydrogen bonding. The catalyst loading was also checked. Lowering the amount of the phosphine oxide catalyst to 5 mol% or 2.5 mol% resulted in similar yields of **2a** (entry 10 and 11). In continuing to decrease the catalyst loading to 1 mol %, it was observed that the yield of **2a** was lowered to 72% even with a prolonged time (6 h, entry 12). As expected, no reaction occurred in the absence of any catalyst (entry 13). As shown in Scheme 1, since HCl could be generated *in situ* from phosphine oxide catalyst and oxalyl chloride, a control experiment was also carried out by performing the reaction in the presence of HCl (2.5 mol%, entry 14). It was observed that 11% yield of **2a** was obtained in HFIP, while no reaction took place in DMF. These results suggested that HFIP played a vital role in this transformation. When Et_3N or Na_2CO_3 was added to the reaction system, only slight decrease in the yield of **2a** was observed, indicating that the in situ generated HCl was not the catalyst but was helpful to the reaction (entry 15). Finally, the amount of oxalyl chloride was also investigated, and 1 equivalent was enough for the reaction (entries 16 – 18).

With the optimized reaction conditions having been established, a series of ketoximes were then evaluated to probe the scope and generality of present protocol. The results were summarized in Table 2. Aromatic ketoximes

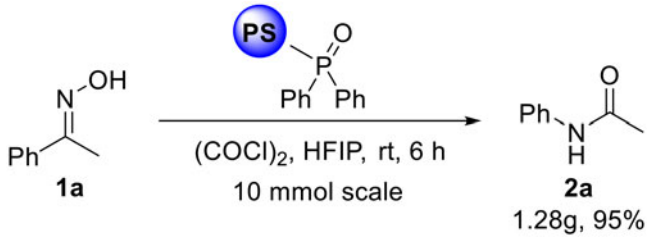
Table 2. Substrate scope[a].





[a]Reaction conditions: **1** (0.5 mmol), HFIP (2 mL), catalyst (2.5 mol%), $(COCl)_2$ (0.5 mmol), room temperature. Isolated Yields.

with functional groups such as methyl, methoxyl and halogen were all well tolerated, affording the desired products in good to excellent yields. The conversion of electron-rich ketoximes was complete within 2 h, while only moderate yield was obtained for the electron-deficient ketoxime (**2g**). No desired product was observed when nitro-substituted ketoxime **1e** was used as the substrate. *Ortho*-substituted ketoximes **1i**–**1k** were found to react smoothly under this protocol to provide the corresponding amides in good to excellent yields by slightly prolonging the reaction time.



Scheme 2. Scale-up experiment.

Meta-substituted ketoxime **1l** and 1-acetonaphthone oxime **1 m** also showed good reactivity, giving the desired products **2l** and **2m** in 95% and 90% yields, respectively. In addition, (*E*)-1-phenylpropan-1-one oxime **1n** was efficiently engaged in the Beckmann rearrangement (**2n**, 93%). Heteroaryl ketoxime **1o** also reacted efficiently to give the desired product **2o** in 75% yield. It was noteworthy that aliphatic oxime **1p** and **1q** survived the reaction conditions albeit in a relatively lower yield (**2p**, 73%; **2q**, 42%).

A scale-up experiment was also performed using (*E*)-1-Phenylethan-1-one oxime **1a** as the substrate (Scheme 2). It was found that this reaction proceeded smoothly to provide the desired product **2a** in 95% yield (10 mmol scale), indicating the practicability of the present protocol. Moreover, the recyclability of the catalyst and solvent is the most important advantages of this protocol. The supported phosphine oxide catalyst could be readily recovered by simple filtration, and HFIP could also be readily recovered by distillation. It should be pointed out that the catalyst could be reused without obvious loss in activity in six consecutive runs (99%, 99%, 99%, 98%, 95% and 92%, respectively).

3. Conclusion

In summary, a polystyrene-supported phosphine oxide-catalysed Beckmann rearrangement of ketoxime in HFIP has been developed. The reactions proceeded smoothly to give the desired products in good to excellent yields except the substrates with strong electron-withdrawing groups. Scale-up experiment could also be achieved under the present protocol. Moreover, ready availability of the catalyst, good substrate compatibility, mild reaction conditions, good reaction efficiency as well as the reusability of the catalyst and the solvent made this procedure complementary to the previous methods.

4. Experimental

4.1. Method and apparatus

Chemicals were used as received without special purification unless stated otherwise. Polystyrene-supported phosphine oxide (1.2–1.8 mmol/g, on polystyrene cross-linked with 2% divinylbenzene) was obtained from Sigma-Aldrich. Thin-layer chromatography (TLC) was visualized using UV light. Column chromatography was generally performed on silica gel (300 − 400 mesh). ^{1}H and 13C NMR were recorded in $CDCl_3$ or DMSO-d_6 at ambient temperature on a 300, 400 or 500 MHz NMR spectrometer. Chemical shifts are reported in δ units, parts per million (ppm). The coupling constants J are given in Hz. All the products are known compounds and were identified by comparing of their physical and spectra data with those reported in the literature (Supplemental Materials, Figures S1–S32).

4.2 Typical procedure for synthesis of compound 2a

Polystyrene-supported phosphine oxide (10.4 mg, 2.5 mol%), (*E*)-1-Phenylethan-1-one oxime **1a** (67.5 mg, 0.5 mmol) and HFIP (2 mL) were added to a 10-mL glass vessel containing a magnetic stirring bar. Then, oxalyl chloride (64.8 mg, 0.5 mmol) was added at 0 °C. The mixture was stirred at room temperature for 2 h. After completion of the reaction (indicated by TLC), the catalyst was removed by filtration and the solvent was removed under reduced pressure. The crude material was purified by silica gel column using PE/EtOAc as the eluent to afford the desired product **2a** in 99% yield.

N-Phenylacetamide **2a**.[11g] White solid, mp 113 − 115 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.01 (t, J = 7.3 Hz, 1H), 2.04 (s, 3H); 13C NMR (125 MHz, DMSO-d_6) δ 168.3, 139.3, 128.6, 123.0, 119.0, 24.0.

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