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Synthesis of *N*-Diphenylphosphinoylimines Using the Kresze Reaction

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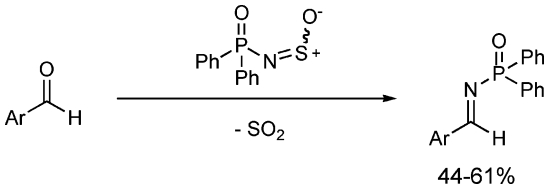

The synthesis of *N*-diphenylphosphinoylimines involving the treatment of aldehydes with *P,P*-diphenyl *N*-sulfinylphosphoramidate ($Ph_2P(O)NSO$) is described. The reagent is prepared from *P,P*-diphenylphosphinic amide, thionyl chloride, and imidazole.

In the past few years, *N*-phosphinoylimines have been extensively exploited in many reactions.[1] Shibasaki has reported the first catalytic asymmetric nitro-Mannich-type,[2] Mannich,[3] and Strecker[4] reactions using these good electrophiles. The phosphinoyl group is also used as a protecting group for amines owing to its facile cleavage under mild acidic conditions.[5] Although the direct condensation of phosphinic amides with highly electrophilic aldehydes constitute a viable entry to *N*-phosphinoylimines, titanium tetrachloride and titanium tetraisopropoxide are usually used as dehydrating reagents to facilitate this condensation.[6,7] In this last procedure, however, the removal of titanium salts can be tedious, and long reaction times (up to 1 day) are sometimes required. Heating the reaction mixture to shorten the reaction times generally led to some degradation of the imines. Stec described the reaction of ketoximes or aldoximes with chlorodiphenylphosphine at low temperature to produce unstable *O*-phosphinyloximes that undergo a rearrangement to give *N*-phosphinoylimines.[8] Our group has reported a method involving the preparation of the sulfinic acid adduct of the imine that decomposes to the imine under basic treatment.[9] This method is particularly effective for the preparation of *N*-diphenylphosphinoylimines derived from alkyl-substituted aldehydes. Inspired by the Kresze reaction,[10] this paper describes a new approach for the synthesis of *N*-phosphinoylimines.

The Kresze reaction is described as the reaction of aldehydes with *N*-sulfinylamines (RNSO)[11] in the presence of a Lewis acid to generate *N*-tosylimines. Using this methodology, Weinreb[12] has reported that the addition of Grignard and organolithium reagents to in situ generated *N*-tosylimines led to protected α-chiral amines (Scheme 1). This transformation involves a [2 + 2] cycloaddition process followed by a SO_2 extrusion.

Given this precedent, we envisioned that this approach should be perfectly amenable to the synthesis of *N*-phosphinoylimines. The Kresze reaction is now applied to the synthesis of *N*-phosphinoylimines **3** using in situ generated *P,P*-diphenyl *N*-sulfinylphosphoramidate[13] **2** and an aldehyde as starting materials (Scheme 2).

The solvent and reaction temperature were optimized using benzaldehyde as starting material (Table 1). Although several solvents can be used for this reaction, toluene provided the best conversions (entry 3).

The methodology was then applied to a variety of aryl-substituted aldehydes. The significant advantage of this procedure is its simplicity: imidazole and freshly distilled thionyl chloride were mixed at −10 °C and stirred at 20 °C for 10 min, and then the imidazolium chloride was filtered off through a fritted glass funnel.[11] A second treatment with thionyl chloride and *P,P*-diphenylphosphinic amide **1**/filtration led to a filtrate that was concentrated to give the crude *N*-sulfinylphosphoramidate. The *N*-sulfinylphosphoramidate was dissolved in toluene, and the aldehyde was added. The solution was stirred typically for 16 h, and evaporation followed by a quick filtration over a small plug of silica gel led to the corresponding *N*-phosphinoylimine with a purity higher than 95% by ^1H NMR. The workup is straightforward and the starting materials are readily available. This procedure is particularly advantageous over the $TiCl_4$ (or $Ti(OEt)_4$) method that requires removal of the titanium derived byproducts through tedious extractions. As shown in Table 2, the reaction occurs well with several aryl-substituted aldehydes. Thus far, we have not been able to extend that reaction to alkyl-substituted aldehydes.

In summary, a new methodology for the synthesis of *N*-phosphinoylimines has been developed. The isolated yields are similar to the methodologies previously developed for the preparation of these compounds. The main advantage of this new procedure is that a straightforward workup is required to isolate the corresponding imine.

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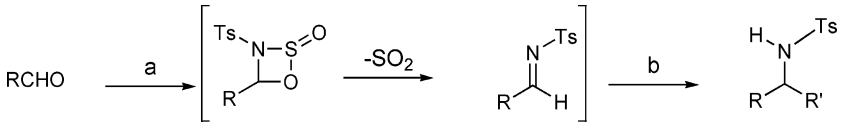
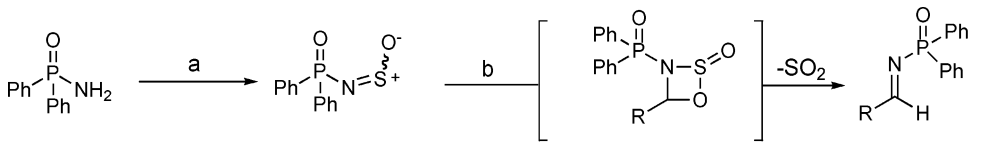
SCHEME 1. Application of the Kresze Reaction toward the Preparation of α-Chiral Amines[a]



[a] Key: (a) TsNSO (1.5 equiv), RCHO (1.0 equiv), 1−2 h; (b) R′M (3.0 equiv), 1 h (32−93%).

SCHEME 2. Synthesis of *P,P*-Diphenylphosphinoyl Imines 3 from Aryl Aldehydes[a]



1 **2** **3** (R = Ar)

[a] Key: (a) imidazole (2 equiv), $SOCl_2$ (2 × 0.5 equiv), CH_2Cl_2, −10 °C to rt, then $NH_2P(O)Ph_2$ (1 equiv); (b) RCHO (1.35 equiv), rt, 16 h, toluene.

TABLE 1. Optimization for the Synthesis of *N*-Phosphinoylimine 3a (R = Ph)

entry	solvent	*T* (°C)	conv[a] (%)
1	THF	rt	57
2	CH_2Cl_2	rt	52
3	toluene	rt	64
4	CH_2Cl_2	55	60

[a] Conversions were determined by ^{1}H NMR and are based on aldehyde consumption.

TABLE 2. Application of Kresze's Reaction to the Synthesis of Different *N*-Phosphinoylimines 3[a]

R	yield (%)
Ph (**3a**)	52
1-naphthyl (**3b**)	48
2-BrC_6H_4 (**3c**)	44
3-$MeOC_6H_4$ (**3d**)	54
4-MeC_6H_4 (**3e**)	61
4-ClC_6H_4 (**3f**)	58
4-$CF_3C_6H_4$ (**3g**)	58
2-furyl (**3h**)	48
2,4,6-MeC_6H_2 (**3i**)	52

[a] Key: (a) RCHO (1.35 equiv), toluene, 16 h, rt.

Experimental Section

Procedure for the Preparation of *P,P*-Diphenyl *N*-Sulfinylphosphoramidate (2). Compound **2** was prepared according to the literature.[13] Thionyl chloride (134 μL, 219 mg, 1.84 mmol) was added to a solution of imidazole (501 mg, 7.36 mmol) in dichloromethane (7.5 mL) at −10 °C. The reaction mixture was stirred at 20 °C for 10 min to form imidazolium chloride, which was filtered off through a fine fritted glass funnel. A second portion of thionyl chloride (134 μL, 219 mg, 1.84 mmol) was added to the filtrate at −10 °C, and the mixture was stirred at 20 °C for 10 min. This solution of *N*-(chlorosulfinyl)imidazole (3.68 mmol) was added via cannula to a solution of *P,P*-diphenylphosphinic amide **1** (800 mg, 3.68 mmol) in dichloromethane (5 mL) at −40 °C. After the reaction was stirred at 20 °C for 6 h, imidazolium chloride was removed by filtration through a fine fritted glass funnel, and the filter cake was washed with dichloromethane (2.0 mL). The filtrate was concentrated to give the crude *N*-sulfinylphosphoramidate **2** as a brown oil which was thermally unstable and moisture sensitive so it was used without further purification.

General Procedure for the Preparation of *N*-Phosphinoylimines 3a−i. The *P,P*-diphenyl *N*-sulfinylphosphoramidate **2** (3.68 mmol) was dissolved in toluene (7.5 mL), and the aldehyde (4.97 mmol) was added. After the solution was stirred at 20 °C for 16 h, the solvent was removed under reduced pressure and the residue filtered through silica gel eluting with 100% AcOEt to afford **3** as a solid, with a purity greater than 95% (^{1}H NMR).

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Supporting Information Available: General information and NMR spectra for compounds described in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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