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Brønsted acid promoted imino-ene reactions

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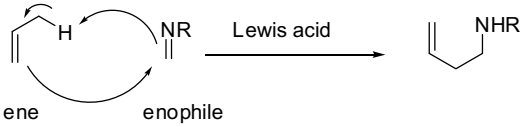
ABSTRACT

A series of all-carbon olefins react with glyoxylate derived imines in the presence of a phosphonic acid through an ene reaction. The isolation of the α-aminoester products is a clear indication that Brønsted acids efficiently promote the imino-ene reaction with hydrocarbon nucleophiles to deliver functionalized α-aminoesters in good yield. The reaction scope and preliminary mechanistic investigations are discussed.

The imino-ene reaction (Eq. 1) provides an elegant entry into the generation of homoallylic amines through the formation of a new carbon–carbon bond between an all-carbon alkene (ene) and an imine (enophile).[1]

Purposeful selection of the ene and enophile components will lead to products containing an olefin and a masked amino acid, both of which endow the substrates with synthetic utility (Fig. 1). A defining advantage of the imino-ene reaction is the ready access to naturally available olefins (ene components) which can permit rapid and cheap access to a series of imino-ene products. The potential of the imino-ene reaction is realized by the Brønsted acid promoted reaction reported herein. The single-step method complements the Lewis acid chemistry as it allows access to amine substrates that are often found to be limiting cases in the traditional Lewis acid catalysis methods.



(1)

The enantioselective Lewis acid catalyzed carbonyl-ene reactions are well documented in the literature.[2,3] The analogous Lewis acid catalyzed imino-ene reactions are also reported to proceed in good yields and high enantioselectivities,[4–7] but the scope of the reaction is limited. The limitation results from significant interactions between a Lewis acid, such as copper, and the starting imine (Fig. 2) or the resulting product amine. Though the interaction is

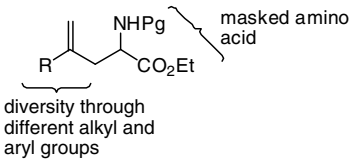


Figure 1. Imino-ene products that feature useful functional groups. Pg = protecting group.

effective for imine activation, it can preclude reactions from occurring. Imino-ene reactions facilitated by Lewis acids require additives to interrupt the chelation[6] or necessitate the use of fluorinated solvents[4] for the reaction to occur to an appreciable extent. The limits of Lewis acid catalysis provide an opportunity to pursue milder imine activation modes. In particular, we chose to effect a hydrogen-bond interaction for activation of the imine.[8,9] The results below show that Brønsted acid activation of the imine, presumably through hydrogen bonding, is an effective method for promoting the imino-ene reaction. The average hydrogen-bond strength between a donor and an acceptor in organic media (1–8 kcal/mol)[10] can be sufficiently activating for reaction to occur although it is significantly weaker than a metal–nitrogen interaction.

Recent literature highlights the use of Brønsted acids as hydrogen-bonding catalysts for activating carbonyl and imine moieties for nucleophilic attack.[11–15] Our preliminary experiments showed that thiourea-,[16,17] urea-, and guanidinium-containing[18–20] compounds were ineffective for the imino-ene reaction; however, phosphonic acids were found to be suitable Brønsted acids for the imino-ene chemistry. Phosphonic acids are reported as

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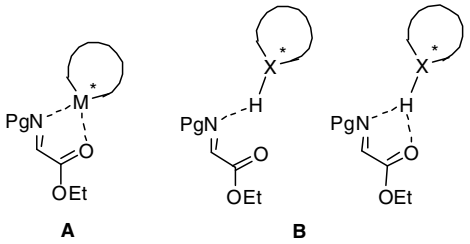
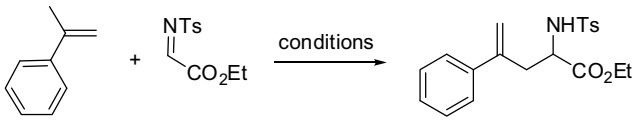


Figure 2. (A) Traditional Lewis acid activation the α-imino ester. (B) Proposed alternative activation though hydrogen bonds. This can occur via a single interaction or a bifurcated interaction. X = heteroatom: Pg = protecting group.

catalysts for reactions involving imine-type substrates,[21–27] including the aza-ene reaction.[28,29] Unlike the reported aza-ene reaction that employs enamines as the ene component, the imino-ene reaction reported herein is the first example of a Brønsted acid-promoted reaction employing unactivated, all-carbon, olefin containing nucleophiles.[30] The reactions proceed in moderate to good yield and do not require air-free techniques.

Optimization of the reaction conditions for the reaction of α-methylstyrene (**1**) and *N*-tosyl-α-iminoester **2** included screening other organic acids, solvents, and reactant ratios (Table 1). This imino-ene reaction proceeds in high yield (90%) in the presence of one equivalent of the phosphonic acid (diethyl phosphate) in CH_2Cl_2 at room temperature (Table 1, entry 1). The increased yield over that of the thermal reaction (42%) (Table 1, entry 2) supports the assertion that the Brønsted acid has a significant role in promoting the reaction. Toluene or THF as the solvent-resulted in little to no yield of the product, thereby identifying dichloromethane as the most suitable medium for the reaction. Noteworthy is the fact that acids such as acetic acid, phosphoric acid, and *p*-toluenesulfonic acid (Table 1, entries 3–5) are ineffective in promoting the imino-ene reaction, thereby confirming the unique role of diethyl phosphate for the highlighted imino-ene reaction.

Table 1
Optimization of reaction conditions for the imino-ene reaction[a]



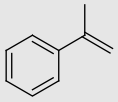
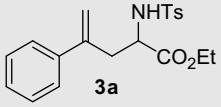
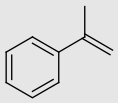
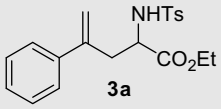
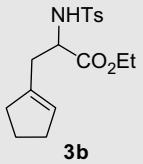
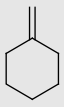
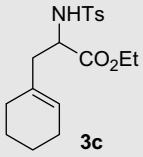
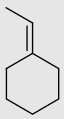
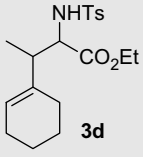
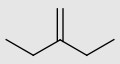
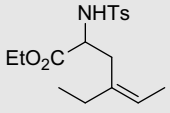
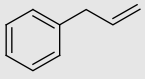
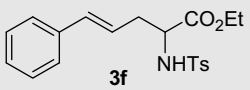
1 **2** **3a**

Entry	Additive (equiv)[b]	Imine (equiv)	Solvent	Yield **3a** (%)
1	Diethyl phosphate (1)	2	CH_2Cl_2	90
2	0	2	CH_2Cl_2	42
Organic Acid				
3	AcOH (0.5)	1	CH_2Cl_2	29
4	H_3PO_4 (0.5)	1	CH_2Cl_2	27
5	*p*-tolSO_2H (0.5)	1	CH_2Cl_2	7
Solvent				
6	Diethyl phosphate (0.5)	1	Toluene	—
7	Diethyl phosphate (0.5)	1	THF	18
Reactants				
8	Diethyl phosphate (1)	1	CH_2Cl_2	61
9	Diethyl phosphate (0.5)	2	CH_2Cl_2	68

[a] All reactions run on a 0.5 mmol scale (1 M) with respect to **1**, except entry 7, which was run on a 1 mmol scale (2 M). All reactions run at room temperature for 48 h.
[b] The commercially available diethyl phosphate can be purchased as 100% pure or as a mixture that contains 25% phosphoric acid. Both produce the same results when used in the imino-ene reaction.

The scope of the imino-ene reaction with respect to the ene component was investigated by using the optimized reaction conditions (Table 1, entry 1). Traditional ene reactants are electron-rich 1,1-disubstituted olefins and all those used for this research react with *N*-tosyl-α-iminoester **2** under the Brønsted acid conditions. Both the α-methylstyrene and cyclopentenyl substrates proceed in good yield (Table 2, entries 1 and 3), and the cyclohexenyl substrates both react to give products in moderate yield (Table 2, entries 4 and 5). The acyclic and 1-substituted olefins (Table 2, entries 6 and 7) are typically poorer ene substrates and the same trend is reflected with our Brønsted acid promoted imino-ene reaction. Alternatively we used diethyl phosphoramidate for some of the above reactions and we noted that reproducible yields of product could be obtained in the presence of 2 mol % of the Brønsted acid, indicating somewhat increased reactivity relative

Table 2
Scope of the imino-ene reaction[a]

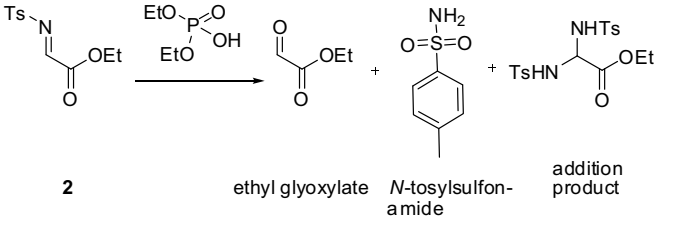
Entry	Ene	Product	Yields[b] (%)
1		 **3a**	90 (42)
2[c]		 **3a**	62
3[d]		 **3b**	91
4		 **3c**	45 (24)
5		 **3d**	39[e]
6		 **3e**	25[e] (25)
7		 **3f**	Trace

[a] All reactions run on a 0.5 mmol scale (1 M) with respect to the alkene at room temperature for 48 h unless otherwise noted.
[b] Yield reported in parentheses are of the isolated product when using diethyl phosphoramidate.
[c] Reaction run for 12 h.
[d] Reported yield is not significantly increased relative to thermal reaction.
[e] The dr = 5:1 as determined by ^{1}H NMR spectroscopy.

to the conditions employing one equivalent of the phosphonic acid. The yields reported herein for an intermolecular imino-ene reaction are significant in light of the fact that (a) the ene component is an all-carbon nucleophile and (b) the proposed mode of activation is a hydrogen bond.

Throughout the optimization of the reaction conditions there were two observations that warranted additional investigation: (1) the optimal conditions required one equivalent of diethylphosphate and two equivalents of imine substrate **2**, and (2) the yield of the isolated product after a 12 h reaction time was moderate (e.g. Table 2, entry 2), but an additional 36 h was required to increase the yield by an additional 30%. To better understand the roles of the components of the reaction we used ^{1}H NMR titrations. Initially, we sought to identify and quantify the interaction between diethyl phosphate and **2**, however we were unable to rigorously identify the presence of a H-bond between the two compounds.[31] A shift in the O*H* peak of diethyl phosphate was observed in *d*-CH_2Cl_2 as incremental amounts of imine **2** were added to the diethyl phosphate solution (note that concentration of the phosphonic acid solution concentration was kept constant). The titration data indicates that imine **2** and diethyl phosphate do not form a clean 1:1 complex (see the Supplementary data). A shift in the O*H* proton was also observed for an experiment in which the diethyl phosphate concentration was incrementally decreased. A plot of the dilution experiment data shows a saturation curve rather than a linear relationship between the O*H* peak shift and the concentration (see the Supplementary data). Together the data suggest the possibility of diethyl phosphate existing in an aggregate state under the reaction conditions.[32,33] Potentially, the two equivalents of imine are needed to interrupt the aggregate state to facilitate the imino-ene reaction.

Additionally, ^{1}H NMR spectroscopy was used to observe a 1:1 mixture of the **2** and diethyl phosphate over a 5 h period to probe any potential reactions that occur in the absence of the ene component. The phosphonic acid indeed appears to promote a hydrolysis reaction of imine **2** as evidenced by the disappearance of the imine peak (δ = 8.17) and the in-growth of an aldehyde-containing compound (δ = 9.35) and a sulfonamide-containing compound. The disappearance of the imine peak and the newly formed aldehyde peak plotted against time is shown in Figure 3. The rate of the disappearance of the imine peak ($t_{1/2}$ = 2 h) is faster than the in-growth of the aldehyde peak, indicating the potential for more than just a simple hydrolysis reaction. ^{1}H NMR evidence and careful isolation and characterization of the components of the reaction mixture confirmed that the imine substrate was reacting in the presence of diethyl phosphate to give three products: ethylglyoxylate, *N*-tosylsulfonamide, and a product derived from the addition of *N*-tosylsulfonamide to **2** (Eq. 2). The fate of the imine in the presence of diethyl phosphate suggests that the potential for multiple reaction pathways makes it necessary to use two equivalents of the imine for the imino-ene reaction to deliver and optimum yield of the α-aminoester products.[34]



(2)

In summary, we have shown that Brønsted acids are effective in promoting an imino-ene reaction in which the ene component is a simple, unactivated olefin. The reaction is proposed to proceed by phosphonic acid activation of the imine to attack by the olefin. We also presented some initial ^{1}H NMR studies that were designed to probe the role of the phosphonic acid, and they suggest that the aggregation state of the acid and the potential for the imine to yield byproducts through other reaction pathways lead to a complex reaction system. The success of the reaction and the preliminary look at physical aspects of the reaction will effectively permit the design of more efficient reaction conditions and catalysts. Investigations into the enantioselective imino-ene reaction will be reported in due course.

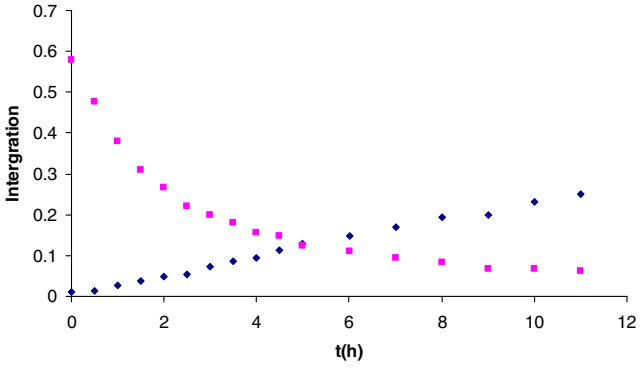


Figure 3. Graphic representation of disappearance of imine and appearance of ethyl glyoxylate. Squares = the integration of imine peak versus time. Diamonds = the integration of in-growth of ethyl glyoxylate versus time.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.075.

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31. The reported pK_a values of simple iminium groups range from 7.9 to 9.5 and the reported pK_a values of dialkyl phosphates are ca. 2. Although the reported pK_a values are valid in aqueous solutions, the difference between the values suggests that it is reasonable to expect a H-bond-type interaction that can activate the imine. For pK_a values, see: Buist, G.J.; Lucas, H.J., J. Am. Chem. Soc. 1957, 79, 6157–6160.
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34. A reaction was run in the presence of molecular sieves and the imino-ene product was isolated in low yield (46%). We are currently investigating whether or not the molecular sieves are absorbing the catalyst and thereby interrupting the reaction. We are also investigating other conditions to rigorously exclude water from the reaction mixture.