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Phosphonic acid catalyzed synthesis of pyrazolidines

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ABSTRACT

A phosphonic acid catalyst has been shown to promote the intramolecular cyclization of acylhydrazone **1**. The resulting heterocyclic products, pyrazolidines, were isolated in good yield for a variety of acylhydrazones. Studies into the role of the phosphonic acid are presented and discussed.

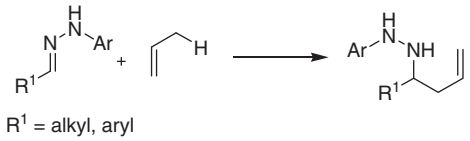
The discovery of methods for the synthesis of complex heterocyclic rings is a major area of interest for organic chemists.[1–4] The ability to develop methods involving the use of phosphonic acid catalysts for making heterocyclic compounds is one goal of our research endeavors. In a previous report we described the use of phosphonic acid as a catalyst for the imino–ene reaction between a glyoxlate-derived imine and a simple alkene.[5] One limitation of our earlier report was the need to use a very reactive imine. Previously, phosphonic acids have been shown to be successful catalysts for a variety of hydrazone-containing substrates.[6,7] Therefore, to expand the scope of our chemistry beyond the reactive imine enophiles, acylhydrazones were introduced as a viable substrate for an imino–ene reaction (Scheme 1). At the outset it was unclear as to whether the imino–ene reaction would predominate over the potential [3+2]-cycloaddition-type reaction,[8,9] for which HCl[10] and chiral zirconium Lewis acid catalysts have been reported.[11,12]

Initially, a citronellal-derived acylhydrazone was synthesized and then reacted under reaction conditions (1 equiv of diethyl phosphate, 2 M in CH_2Cl_2, 25 °C, 48 h) similar to our previously reported imino–ene chemistry.[5] The reaction did not deliver the expected hydrazine **3a** (Scheme 2a), but instead a pyrazolidine derivative (**2a**) was isolated (76% yield) as the major product (Scheme 2b). The pyrazolidine product was the product of the competing [3+2] cycloaddition.

The isolation of the pyrazolidine product **2a**, though not unexpected, warranted additional investigation because such ring systems can be easily converted into 1,3-diamines after N–N bond cleavage[12] to generate useful synthons. Chiral 1,3-diamines have utility as chiral ligands for asymmetric catalysis,[13] as well as biologically important cisplatin derivatives.[14] Given our interest in the reaction and the utility of the products we chose to further examine this reaction in terms of reaction optimization as well as mechanistic aspects.

Given the moderate product yield of the trial reaction the full potential of this reaction was explored by varying several reaction parameters including the acid catalyst, the number of equivalents of catalyst, temperature, and concentration (see the Supplementary data for full details). Using the same reaction conditions (see Scheme 2) at 4 °C resulted in a decreased product yield (56%). Additional systematic changes results indicated that using a 0.5 M reaction solution (with respect to the hydrazone) at 4 °C was optimal for the reaction, thus delivering the product in an 83% yield. The isolated product was a diastereomeric mixture[15] that contained only two out of a possible four diastereomers, thus demonstrating good selectivity.[12,16] In part this selectivity arises from the intramolecular nature of the reaction as it benefits from favorable entropic factors. Interrogation of the system with regard to reaction time was expected to shed some light on the distribution of the product stereoisomers (Table 1).

At 6 h, the reaction yielded over half of what was made at 48 h and the dr value is at its highest (compare entries 1 and 3 in



R^1 = alkyl, aryl

Scheme 1. A proposed general ene reaction between a hydrazone and an ene.

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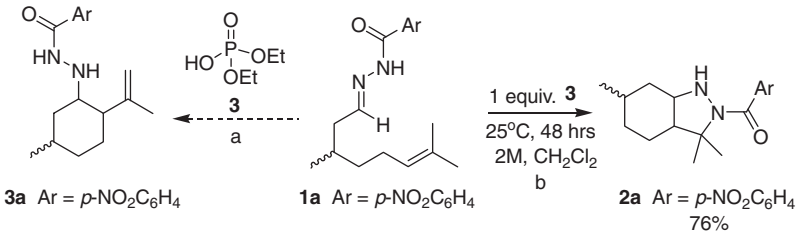
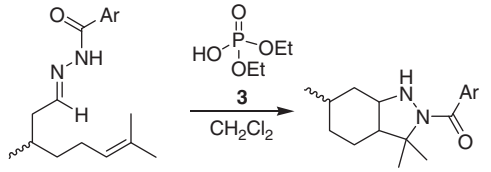


Scheme 2. (a) Ene reaction of an acylhydrazone to produce hydrazine derivative. (b) Cyclization of an acylhydrazone to form a pyrazolidine derivative.

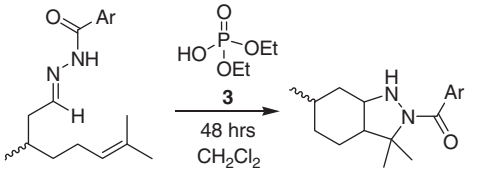
Table 1
Effect of time on the cyclization reaction



Entry[a]	Equiv of **3**[b]	Time (h)	Temp (°C)	Yield (%)	dr[c]
1	1	6	4	47	1:4.4
2	1	12	4	62	1:3
3	1	48	4	83	1:3
4	0.25	48	25	64	1:2.8

[a] All reactions were run at 0.5 M based on **1a**.
[b] The phosphonic acid used was synthesized and contained a 25% impurity of crystalline H_3PO_4 dissolved in it.
[c] Determined by ^1H NMR integration.

Table 2
Effect of additional Brønsted acids on cyclization reaction



Entry[a]	Equiv of **3**	Additive	Equiv of additive	Yield (%)	dr[d]
1	0	H_3PO_4[b]	1	12	1:4.8
2	0.75	H_3PO_4[b]	0.25	74	1:3
3	0.75	H_3PO_4[c]	0.25	78	1:2.6
4	0.75	H_2SO_4	0.25	67	1:3.3
5	0.75	CH_3COOH	0.25	60	1:2.9

[a] All reactions were stirred at 4 °C at a concentration of 0.5 M based on **1a**.
[b] Crystalline acid.
[c] 85% acid.
[d] Determined by ^1H NMR integration.

Table 1). The yield at 12 h increased about 20% more than that obtained after 6 h of reaction time (Table 1, entry 2). In all cases the dr value remained the same within error. When the equivalents of acid were lowered to 0.25 equiv, and stirred for 48 h at 25 °C, the product was formed in moderate yield, which was comparable to that of the reaction after 12 h using a full equivalent of acid (Table 1, entry 4). Importantly the dr value does not vary greatly, thus indicating that there is no equilibration in play and that the reaction is under thermodynamic control.

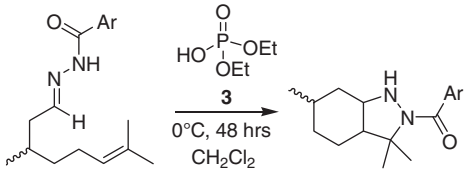
An important aspect of this reaction is the phosphonic acid used. It was clear from early experiments that pure phosphonic acid was a poor catalyst. The presence of a small amount of H_3PO_4 was necessary to deliver the high product yields; therefore we investigated the role of the acid as well as the potential for using other acids as additives (Table 2).[16]

H_3PO_4 alone is not an effective catalyst (Table 2, entry 1), but when combined with the phosphonic acid the cyclization product is isolated in good yield (Table 2, entries 2 and 3), albeit with a lower dr value. The yield is similar regardless of whether crystalline or hydrated H_3PO_4 is used. Notably, when either H_2SO_4 or AcOH is used in combination with the phosphonic acid the reaction proceeds with moderate yield (Table 2, entries 4 and 5). HCl was also used as a co-catalyst with **3**, but the reaction proceeded in low yield (44%).[17] These results highlight the importance of the phosphonic acid, as well as show that the better catalyst system for this reaction involves a combination of diethyl phosphate and phosphoric acid.

To explore the importance of the electronic nature of the acylhydrazone, a series of citronellal-derived acylhydrazones was tested wherein the substituent of the 4-position of the aryl ring was varied (Table 3).

The results clearly indicate that the electron-withdrawing character of the group on the 4-position of the aryl ring is crucial for

Table 3
Electronic effects on the cyclization

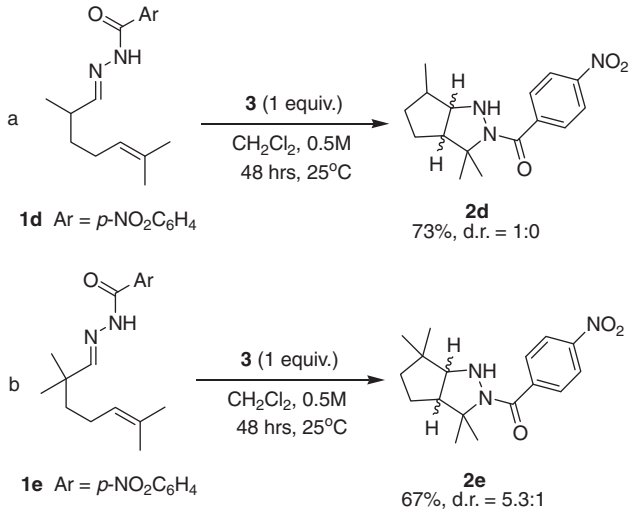


Entry[a]	Hydrazone	[**1**] (M)	Equiv **3**[b]	Yield (%)
1	**1a**	0.5	1	82
2	**1b**	0.5	1	44[c]
3	**1c**	1.0	1	28

[a] All reactions were run at 0 °C for 48 h in dichloromethane.
[b] The commercially available diethyl phosphate was used with 25% phosphoric acid impurity.
[c] The major diastereomer was determined to have a *trans*-ring junction. See the Supplementary data for full details.[18]

cyclization to occur in high yield. The reaction with the ring bearing and OMe group is the lowest yielding substrate (Table 3, entry 3). This trend in reactivity is in keeping with the notion that the electron-withdrawing groups activate the C=N group for nucleophilic attack (see below for mechanistic discussion).

Acylhydrazones having substitutions α to the imine carbon atom were synthesized to explore the steric tolerance of the cyclization. These acylhydrazones were expected react to form two



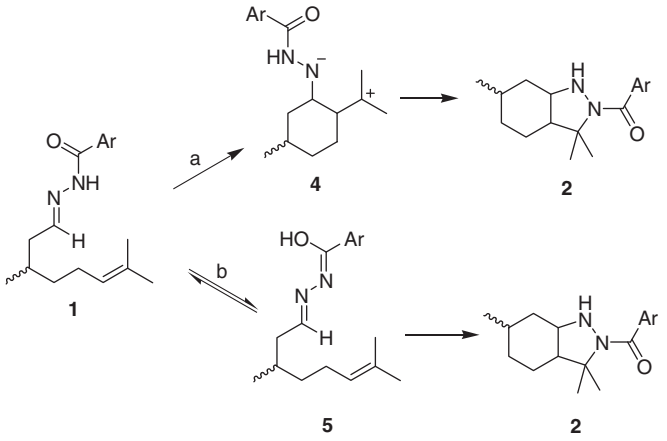
Scheme 3. Scope of the reaction with (a) alpha-methyl acylhydrazone and (b) alpha-dimethyl acylhydrazone. ^{1}H NMR was used to determine dr ratio, however the major diastereomer has not been fully characterized.

fused five-membered rings instead of the fused ring system observed with the citronellal acylhydrazone. The reaction of α-methyl acylhydrazone **1d** proceeded with good yield and excellent diastereoselectivity when using 1 equiv the catalyst (Scheme 3a). A similar result was found with the α-dimethyl acylhydrazone **1e** (Scheme 3b). Notably, the reaction proceeds well when using other acylhydrazones to generate heterocycles containing fused five-membered rings. Additionally, the substitution at the carbon atom α to the hydrazone carbon center has little effect on the reaction yield, but does affect the selectivity of the reaction. The introduction of one methyl group is sufficient to selectively deliver one stereoisomer, and although the introduction of a second methyl group results in a 5.3:1 dr value, it suggests that the additional methyl group is enough to diminish the selectivity.

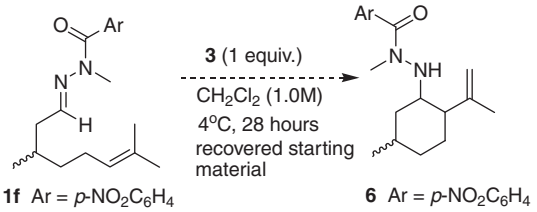
Collectively the data confirmed the role of the phosphonic acid as a catalyst for the cyclization reaction and indicated that a stereoelectronic effect was present. A closer look at mechanism for the reaction revealed two possible mechanistic pathways that the cyclization could undergo: (1) a stepwise cyclization (Scheme 4a), or (2) a concerted [3+2] cycloaddition (Scheme 4b).[11,19] In the stepwise reaction, a nucleophilic addition generates carbocation **4** and then successive cyclization leads to the pyrazolidine product **2**. In the [3+2] cycloaddition, a 1,3-dipole, possibly in the tautomer form **5**, reacts in a concerted manner with the olefin. Reported mechanistic studies[11] with the analogous Lewis acid catalyzed cyclization of acylhydrazones suggest that the mechanism proceeds in a concerted manner, but an additional investigation is necessary to see if this applies to the Brønsted acid cyclization reaction.

A preliminary experiment was conducted to test the methylated acylhydrazone **1f**. The presence of the methylated nitrogen atom was expected to preclude the tautomerization to the more reactive 1,3-dipole substrate, therefore reducing the nucleophilicity of this nitrogen atom. It was expected that if this reaction was stepwise, the first addition would occur and perhaps the formal ene product **6** would be observed (Scheme 5). However, neither this product, nor any cyclization product was observed under Brønsted acid conditions, suggesting that perhaps the NMe group prevented the interaction of the substrate with the phosphonic acid, thereby completely shutting down its reactivity.

In an attempt to learn more about the interaction between the catalyst and the acylhydrazone substrate ^{1}H NMR spectroscopy was used to identify and quantify this interaction. Previous work



Scheme 4. (a) A step-wise cyclization and (b) a concerted [3+2] cyclization of an acylhydrazone to form a pyrazolidine derivative.



Scheme 5. Proposed ene product when a methylated acylhydrazone was subjected to phosphonic acid conditions.

indicated that the signal corresponding to the –OH proton of the phosphonic acid shifted as the concentration changed.[20,21] For this reason, the concentration of diethyl phosphate was kept constant while the hydrazone **1a** was added incrementally (concentrations of 0.002 M–0.5 M; see the Supplementary data). A change in the shift of the NH proton on the hydrazone confirmed an interaction between **3** and **1a**. Consequently, Job plot analyses (see the Supplementary data) were employed to identify the stoichiometry of the catalyst–substrate interaction. The Job analysis was run using ^{31}P NMR spectroscopy data and indicated that the interaction between the acylhydrazone and phosphonic acid is not a clean 1:1 interaction as there is potentially aggregation or ternary-type complexes arising from the presence of the phosphoric acid. The data confidently supports the proposal that the phosphonic acid interacts with the acylhydrazone substrate to effect cyclization and our proposed substrate–catalyst interaction is shown in Figure 1.

In summary we have described a detailed study of the phosphonic acid catalyzed reaction of acylhydrazones to generate heterocyclic rings. The chemistry reported herein adds yet another example of phosphonic acid catalysts promoting reactions of acylhydrazones to the organocatalysis literature. Currently, our studies have been restricted to hydrazones containing alkyl substituents on the olefin, and we plan to study hydrazones having various substitutions on the olefin, such as those containing aryl groups. The

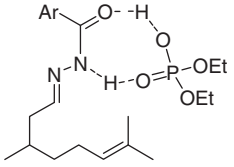


Figure 1. Proposed interaction between acylhydrazone and phosphonic acid **3**.

development of the reaction into a general method for simple access to heterocycles holds promise given the studies into the reactions parameters presented herein.

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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.2011.11.083.

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15. The major product was determined to have a cis ring junction (see Supplementary data for crystal structure). The minor product has not been fully characterized.
16. Preliminary attempts have been made to test other phosphonic acids with varying ester moieties. The cyclization of hydrazone **1a** under conditions similar to those in Table 1, entry 3 with dibutyl phosphate (without H_3PO_4) yielded 54% of **2a** with a dr value of 1:1.6. The cyclization of **1a** under conditions similar to those in Table 1, entry 3 using diphenyl phosphate (without H_3PO_4) resulted in a 26% yield with only the major diastereomer observed. The study of this interesting observation will be a topic for future work.
17. 0.75 equiv of **3** and 0.25 equiv of HCl were used at 0.5 M in CH_2Cl_2 at 0 °C for 48 h.
18. CCDC number 834529 (**2a**) and 833013 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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