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Investigation and Application of Amphoteric α-Amino Aldehyde: An in Situ Generated Species Based on Heyns Rearrangement

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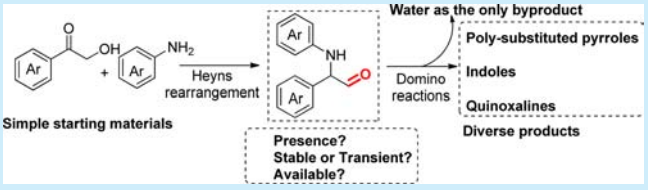
Supporting Information

ABSTRACT: In situ generation of the reactive amphoteric α-amino aldehyde with simple α-hydroxy ketones and phenylamine via Heyns rearrangement was proven to be feasible. Metal-free domino reactions based on this reactive intermediate were effectively used to afford important N-heterocycles including polysubstituted pyrroles, indoles, and quinoxalines conveniently. A simple starting material, water as the only byproduct, and diversity of the useful products will make this method greatly attractive for pharmaceutics.



The creation of molecular complexity and diversity from common starting materials while combining economic and environmental aspects constitutes a great challenge in modern organic chemistry from academic and industrial perspectives.[1] In this regard, organo catalytic domino reactions, which can rapidly form complex molecules from readily available substrates in a single operation without isolation of intermediates, have emerged as powerful tools to reach this near-ideal goal.[2] During the past few years, considerable efforts have been made to develop catalytic domino transformations.[3] However, the design of new selective cascade reactions is a continuing challenge at the forefront of organic chemistry.

The Amadori and Heyns rearrangements have been known to carbohydrate chemists for decades (Figure 1, eq 1). Both reactions suffer from a variety of preparative shortcomings such as separation drawbacks, side reactions, further degradation entering into the Maillard reaction cascade, etc. Therefore, this rearrangement appears to be highly underrated as a useful method for synthetic chemists.[4] Recently, this rearrangement was extended to the synthesis of α-amino ketones with α-hydroxy ketones and a suitable amine as starting materials.[5]

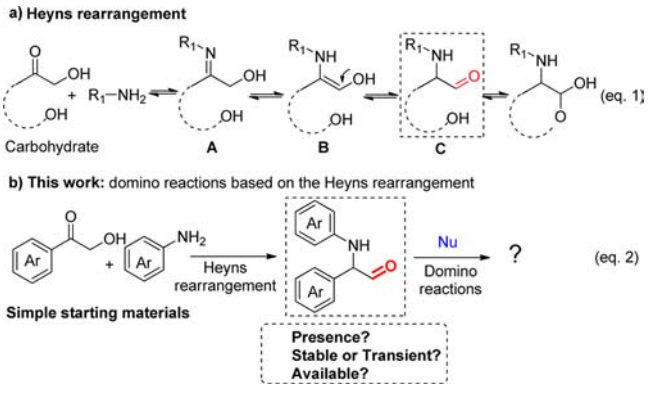


Figure 1. Domino reactions based on α-amino aldehyde generated through Heyns rearrangement.

We realized that the key intermediate formed in this tandem reaction was α-amino aldehyde **C** resulted from the rearrangement of imine **A** to enolamine **B** and the subsequent reprotonation (Figure 1, eq 1). The Heyns rearrangement proceeded on the basis of the capture of the aldehyde with intramolecular hydroxy. Here are our questions: What will happen when other nucleophiles were used? What product would be formed through this domino reaction process with simple α-hydroxy ketone as substrate (Figure 1, eq 2)? Herein, we report a type of efficient domino reaction based on the amphoteric α-amino aldehyde formed from simple α-hydroxy ketone and phenylamine, which allowed for the fast synthesis of N-containing heterocycles including pyrrole, indole, quinoxaline, etc.

To verify our idea of application of the α-amino aldehyde, our initial investigation was focused on the presence and the availability of this intermediate. Interestingly, the characteristic signal of enolamine intermediate **B** and the α-amino aldehyde intermediate **C** could be observed directly through NMR spectroscopy (Figure 2). Both intermediates **B** and **C** enriched constantly from 1 to 5 h; meanwhile, the ratio of **B** to **C** changed from 11/1 to 2/1 gradually. Those results demonstrate that the imine **A** formed by the combination of α-hydroxy ketone and *p*-anisidine could isomerized into the enolamine **B** easily, which is understandable as the enol structure could be stablized by the formation of a conjugation system with a *p*-methoxyphenyl group. However, the direct observation of the accumulation of **C** through conversion from intermediate **B** on NMR spectroscopy is beyond our expectations, suggesting the

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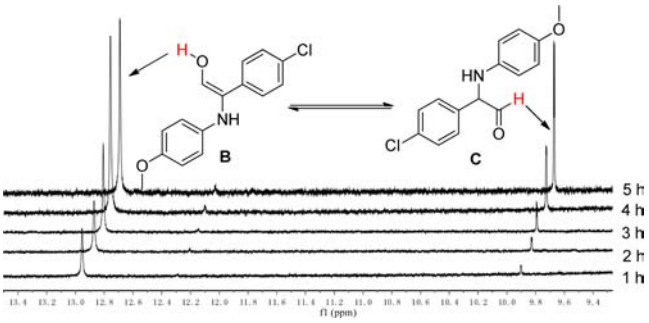


Figure 2. Investigation of the in situ generated α-amino aldehyde via NMR.

transformation from the starting α-hydroxy imine **A** to α-amino aldehyde intermediate **C** is not only feasible but easy to realize.

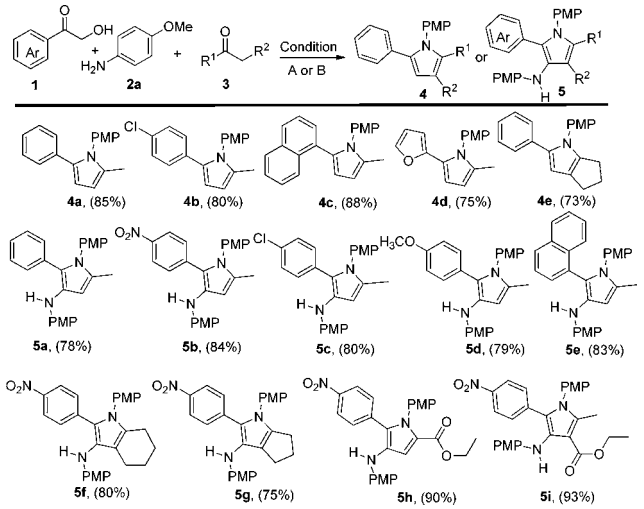
Based on the above results, we then began to screen proper nucleophiles to react with the in situ formed α-amino aldehyde. Initially, acetone was chose to react with α-hydroxy ketone **1a** and *p*-anisidine **2a**. The result was interesting, for substituted pyrrole **4a** was obtained in 29% yield (Table S1). Pyrroles, one of the most valuable N-heterocyclic compounds, constitute the core motif of natural product and medicinal agents.[6] These properties continue to stimulate interest in the development of new synthetic methods for pyrroles. Traditional methods for pyrrole synthesis include the Knorr, Hantzsch, and Paal−Knorr syntheses.[7] Recently, many metal-catalyzed methods for the synthesis of pyrroles have been reported.[8] However, the development of an efficient method that provides highly substituted pyrroles from readily available feedstock, especially in an atom- and step-economic manner, still remains challenging and highly desirable.

Therefore, we decided to optimize the three-component domino synthesis of pyrroles (Table S1). The yield of **4a** increased enormously to 85% after the reaction temperature was raised under anhydrous and anaerobic toluene. We then extended the reaction to different α-hydroxy ketones under the optimal conditions, which afforded the corresponding pyrrole **4** with preferable yield (75−88%) (**4b−d**, Scheme 1). Notably, using cyclic ketone as the nucleophile afforded the corresponding pyrrole as well (**4e**, Scheme 1).

The above results demonstrated that the in situ formed amphoteric α-amino aldehyde could be efficiently attacked with ketone to afford polysubstituted pyrroles. We reasoned that the α-amino aldehyde could form imine with another equivalent of amine as well, which might be attacked by ketone to afford the Mannich reaction product. Moreover, making the reaction selectively occur in this way might be very interesting. We then re-examined the reaction with α-hydroxy ketone **1a**, *p*-anisidine **2a**, and acetone **3a**, using PTSA as catalyst, but this time 2 equiv of amine **2a** was used (Table S2). After clear and careful separation of the reaction mixture, we found the substituted pyrrole **5a** (32% yield) accompanied by **4a** (29%) as the major byproduct (Table S2).

As we know, highly substituted pyrroles are useful pharmaceutical intermediates, especially those with amino group substituents.[9] Therefore, the yield of pyrrole **7a** was increased to 78% after screening catalysts and optimizing the reaction conditions (Table S2). Strikingly, small organocatalyst prolineamide **Ca1** was found to catalyze the reaction effectively, affording pyrrole **5** exclusively. Then the generality of this reaction was explored. On one hand, different α-hydroxy

Scheme 1. Domino Reaction Based on Intermolecular Carbon Nucleophiles[a,b]



[a]Conditions A for obtaining **4**: 0.2 mmol of **1**, 0.24 mmol of **2a**, 0.01 mmol of PTSA, and 50 mg of 4 Å molecular sieves were reacted in 2 mL of acetone (0.6 mmol of **3** in 2 mL of toluene for other ketones) at 60 °C under argon for 48 h. Conditions B for obtaining **5**: 0.2 mmol of **1**, 0.44 mmol of **2a**, 0.02 mmol of **Ca1**, and 0.6 mmol of ketone (for acetone, acetone/DMSO, 1/4 was used) were reacted in 2 mL of DMSO at 50 °C under air for 48 h. [b]Aromatic amines with electron-withdrawing substituents could not be used to afford the corresponding products.

ketones with electron-withdrawing or -donating groups were examined, which afforded the corresponding pyrrole **5** with moderate to high yield (79−84%) (**5b−e**, Scheme 1). On the other hand, different types of ketones were investigated. For cyclic ketones including cyclohexanone and cyclopentanone, the corresponding all-substituted pyrroles **5f** and **5g** were obtained conveniently. Strikingly, α-carbonyl ester or β-carbonyl esters were effectively employed to afford the corresponding pyrroles **5h** and **5i** with excellent yield and high regioselectivity (Scheme 1). Interestingly, aromatic amines with electron-withdrawing substituents could not be used to afford the corresponding products.

Based on the reaction results for synthesis of the two types of pyrroles, we proposed reasonable reaction mechanisms (Figure 3). First, the ketone imine **A1** was formed by dehydration of **1a** and **2a**, which tautomerized to enamine **B1**. Then the key intermediate **C1** was generated through enol−aldehyde tautomerization with **B1**. Next, the in situ formed α-amino aldehyde **C1** could react in two ways: (1) formation of imine **D1** and occur Mannich reaction with acetone to produce β,γ-

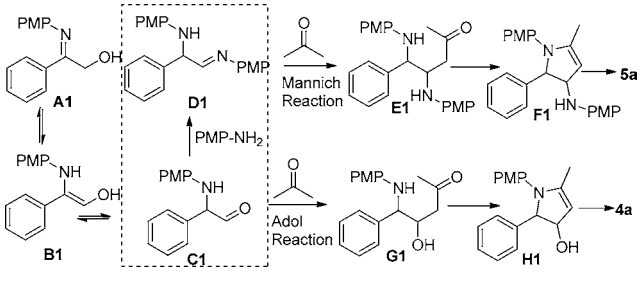


Figure 3. Reasonable reaction mechanism for the domino synthesis of two types of pyrroles.

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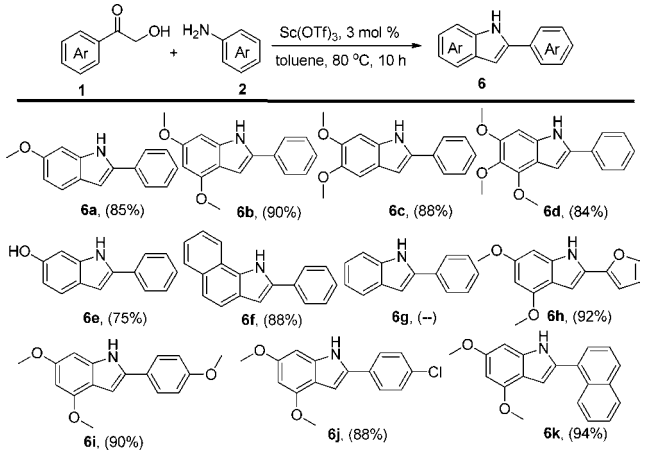
diamine ketone **E1** or (2) direct reaction with acetone to obtain β-hydroxy-γ-amino ketone **G1**. However, the expected intermediate continued to cyclize by dehydration and isomerization to **F1** and **H1**, respectively. Finally, the 2,3-dihydropyrrole **F1** was converted to **5a** by dehydrogenation due to the driving force of aromatization, while **4a** was formed due to dehydration of **H1**. Interestingly, the only byproduct during the above domino synthesis of pyrroles was water.

Encouraged by the successful synthesis of pyrroles with intermolecular carbon nucleophiles, our attention turned to the possibility of trapping the α-amino aldehyde with intramolecular carbon nucleophiles. Therefore, the reaction between 3-methoxyphenylamine **2b** and α-hydroxy ketone **1a** was investigated (Table S3). Interestingly, indole **6a** was obtained through the Freidel–Crafts reaction of the in situ generated amphoteric α-amino aldehyde. As a result, we examined the reaction by optimizing the reaction conditions and investigating the reaction scope (Scheme 2 and Table S3). In general,

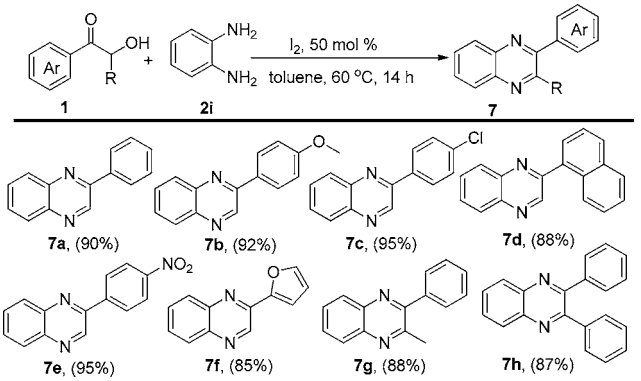
Scheme 2. Domino Reaction Based on Intramolecular Carbon Nucleophiles



electron-rich aromatic amine could effectively react with α-hydroxy ketone to afford the corresponding 2-arylindoles with excellent yield (Scheme 2, **6a–f,h–k**). Notably, the Friedel–Crafts reaction selectively occurred at the *para* position to afford indoles **6a** and **6e** effectively with the corresponding amine as substrate. However, when phenylamine was used with electron-donating groups as substrate, the desired indole **6g** was not obtained. Compared with the previous methods, which involved the complex substrates and transition metal as catalyst,[10] the synthetic method developed here could be used as a mild and efficient alternative to rapid assembly of indole with high atom efficiency.

The above investigation revealed that carbon nucleophiles could effectively trap the transient amphoteric α-amino aldehyde formed in situ. We then wondered whether nitrogen could be applied as nucleophile. We reasoned that the aldehyde intermediate could condense with another intramolecular amino group to afford quinoxaline derivatives, assuming that *o*-phenylenediamine **2i** was used as substrate[11] (Scheme 3). To our delight, we finally succeeded in preparation of quinoxaline **7** efficiently after optimizing the reaction conditions (Table S4). Quinoxaline **7a** was eventually obtained with 90% yield under the optimal conditions. Then the reaction scope was investigated with various α-hydroxy ketones. In general, the reaction proceeded smoothly and afforded the corresponding

Scheme 3. Domino Reactions Based on Intramolecular Nitrogen Nucleophiles



quinoxalines with excellent yield (85–95%) (**7b–f**, Scheme 3). Strikingly, 2,3-disubstituted quinoxalines were obtained using the corresponding α-hydroxy ketone as substrates (**7g,h**, Scheme 3), in which transient α-amino ketone might be involved.[5]

The above two examples demonstrated once again that the in situ generated amphoteric α-amino aldehyde has diversity applications in domino synthesis of N-heterocycles. Therefore, we asked the following questions: (1) Why was the α-amino aldehyde **C1** efficiently formed from **A1** catalyzed by acids under our reaction conditions? (2) Why did the domino reaction processes efficiently occur with this intermediate? First, we chose Hantzsch ester (HEH) to trap the possible intermediate (Figure 4).[12] The most likely product, amino

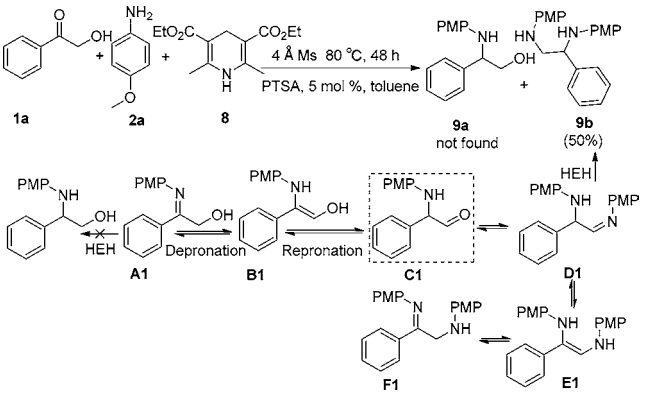


Figure 4. Investigation of reaction process via transfer hydrogenation.

alcohol **9a**, from transfer hydrogenation of α-hydroxy imine **A1** was not detected. On the contrary, vicinal diamine **9b** was obtained as the exclusive product with 50% yield, proving the ketone imine **A1** could be easily transformed into α-amino aldehyde **C1** through more stable intermediate enolamine **B1** (Figure 4). The formation of aldimine **D1** was the driving force for the domino reactions, affording the vicinal diamine **9b** exclusively. Second, different types of 3,3′-disubstituted chiral BINOL-phosphoric acid were used to catalyze the transfer hydrogenation reaction. The results revealed that chiral phosphoric acids with different substituents catalyzed the reaction with similar enantioselectivity (20% ee) (see Figure S4). To the best of our knowledge, those catalysts were successfully used for asymmetric transfer hydrogenation of ketone imines.[13] Those results verified again that the transfer

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hydrogenation by HEH tend to occurred on aldimine **D1** rather than ketone imine **A1** due to the fast transformation through α-amino aldehyde intermediate **C1**. The chirality obtained probably arose from asymmetric protonation (**B1** to **C1** or **E1** to **D1**) rather than asymmetric transfer hydrogenation of ketone imine **F1** (Figure 4).

In summary, amphoteric α-amino aldehyde could be generated in situ with readily available starting materials via the Heyns rearrangement. This transient intermediate was proven to be available through several domino reactions. For the traditional Heyns rearrangement, the in situ formed α-amino aldehyde was captured by the intramolecular hydroxyl. However, we succeeded in capturing this reactive intermediate through intermolecular or intramolecular carbon nucleophiles and nitrogen nucleophiles. Different types of pyrroles, especially all-substituted pyrroles, 2-arylindoles, and quinoxalines, were smoothly obtained with this efficient domino reaction. Interestingly, the methods developed herein allowed for the fast synthesis of four types of N-heterocycles based on one in situ formed amphoteric α-amino aldehyde. Meanwhile, the only byproduct formed in these domino reactions was water. These results may pave the way for using simple α-hydroxy ketone as the precursor of α-amino aldehyde, which would be used as important synthon in synthetic chemistry in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02133.

Experimental procedures; characterization of selected compounds (PDF)

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Notes

The authors declare no competing financial interest.

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