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Acid promoted dimerization of β-amino-α,β-unsaturated amides affording bis(functionalized) pyrrolinones

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ABSTRACT

Polysubstituted pyrrolinones were synthesized by the dimerization of 3-amino-2-butenamides via treatment with 0.5 equiv *p*-TsOH under mild reaction conditions, including oxidation and 1,2-migration of the methyl group. This method is practically advantageous compared to the conventional methods for the preparation of pyrrolinones, because it does not require difficult experimental manipulations and special reagents such as metal catalysts and oxidants. Because the structures of β-amino-α,β-unsaturated amides can be easily modified by changing the precursors, β-keto amide and amine, synthesis of diverse pyrrolinones is possible.

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Pyrroline-4-ones are one of the attractive frameworks because these scaffolds are widely found in optical materials[1] and biologically active compounds such as HIV-1 protease inhibitors,[2] antimalarials,[3] and antimicrobials.[4] Despite the highly valuable and versatile applications, only a few synthetic methods have been reported for pyrrolinones. The most common approach to synthesize pyrrolinones is condensation of α-amino acid esters with aldehydes, facilitating stereo-controlled synthesis (Scheme 1, Method A).[5] The formal [3+2] cycloaddition reactions of diphenylcyclopropenones with imines (Method B) and α-diazoimines with ketenes have also been used for this purpose.[6] The transition-metal-catalyzed intramolecular cyclization of α-aminoynones and the condensation of imines with vicinal tricarbonyl compounds are acceptable methods (Methods C and D).[7,8] However, these methods suffer from some drawbacks such as low availability of the starting materials and narrow substrate scope. Furthermore, it is difficult to introduce multiple functional groups into the pyrrolinone framework. Thus, the development of a facile method for multifunctionalized pyrrolinones remains one of the challenging projects.

Recently, we reported a systematic study on the regioselective amination of acetoacetamides (3-oxobutanamides).[9] The reaction with less hindered amines involved condensation at the β-keto moiety, affording 3-amino-2-butenamides while the reaction with bulky amines involved substitution at the amide moiety. Aminobutenamides may serve as useful building blocks in the organic synthesis because of both multifunctionality and the biased electron density of the carbon-carbon double bond also known as push-pull alkene.[10] During our studies on chemical conversion of aminated enamides, polysubstituted pyrrolinone were obtained when exposed to air at room temperature. A similar dimerization of enamides has been reported by two groups: hypervalent iodine(III)-mediated cyclization (Scheme 2, Method E) and Cu(II)-catalyzed oxidative tandem cyclization (Scheme 2, Method F).[11,12] Although bis(functionalized) pyrrolinones can be prepared in good yields by these protocols, highly toxic trifluoroacetic acid is used in both the cases, and substituents can be present on the amide function of aryl groups. Contrary to these methods, the present dimerization proceeded at room temperature without using any special reagent. This advantageous feature encouraged us to study this reaction in detail for developing a practical method for the synthesis of polyfunctionalized pyrrolinones.

The substrates, 3-amino-2-butenamides **1**, were easily prepared in 76–97% yields by heating acetoacetamide with amines such as propylamine isobutylamine, *sec*-butylamine and benzylamine at 60 °C for 3 h in THF. When 3-propylamino-2-butenamide (**1a**) was exposed to air at room temperature for 3 days, crystalline precipitates were obtained in the chloroform solution. Based on spectral data, this crystalline product was determined to be 1-propyl-2,5-dimethyl-3-oxo-2,3-dihydro-1*H*-pyrrole-2,4-dicarboxiamide (**2a**), a dimeric product of **1a**, and the structure was finally confirmed by

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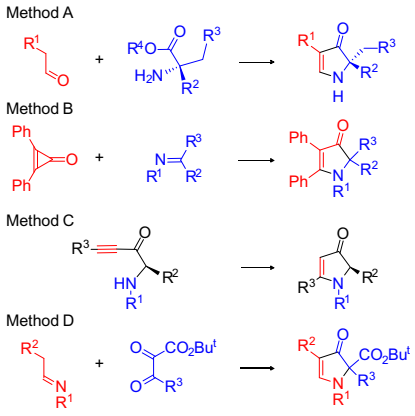
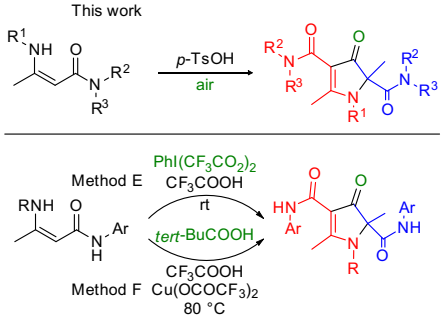


Scheme 1. Commonly used synthetic methods for pyrrolin-4-ones.



Scheme 2. Three kinds of dimerization of β-amino-α,β-unsaturated amides.

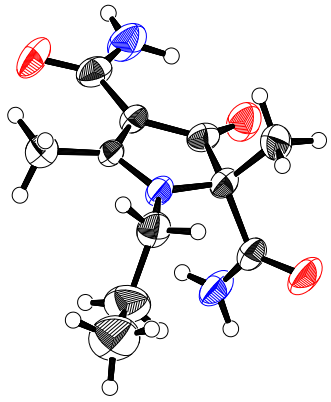
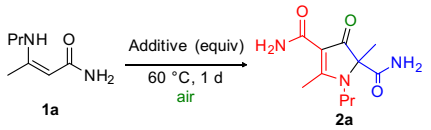


Fig. 1. ORTEP diagram of the molecular structure of **2a**.

X-ray crystallography (Fig. 1). This structure indicates that the dimerization involved the oxidation of the pyrroline framework and 1,2-migration of the methyl group.

First, we optimized the reaction conditions using butenamide **1a** as the model substrate. Among several solvents such as hexane, benzene, chloroform, ethyl acetate, and acetonitrile, nonpolar benzene was effective for the dimerization (Table 1 entries 1–6). Although this reaction proceeded even in the absence of any additives, the addition of *p*-toluenesulfonic acid (*p*-TsOH) significantly accelerated the reaction. Notably, the amount of *p*-TsOH was crucial for this dimerization, and 0.5 equiv *p*-TsOH afforded pyrrolinone **2a** in the best yield (entries 7–11, Fig. 1). When ⩽0.5 equiv of *p*-TsOH was used, the starting material **1a** was recovered. In contrast, acetoacetamide, the hydrolized product of **1a**, was obtained when more than 0.5 equiv of *p*-TsOH in the reactions (Fig. 2).

Table 1
Optimization of reaction conditions for synthesis of pyrrolin-4-ones **7Aa**.



Entry	Solvent	Additive	Yield (%)
1	Hexane	–	12
2	Benzene	–	24
3	Chloroform	–	17
4	Ethyl Acetate	–	9
5	Acetonitrile	–	3
6	Methanol	–	6
7	Benzene	*p*-TsOH (0.2)	45
8	Benzene	*p*-TsOH (0.4)	70
9	Benzene	*p*-TsOH (0.5)	92
10	Benzene	*p*-TsOH (0.7)	48
11	Benzene	*p*-TsOH (1.0)	0
12[a]	Benzene	*p*-TsOH (0.5)	Trace
13	Benzene	*p*-TsOH (0.5)/TEMPO (5.0)	80
14	Toluene	*p*-TsOH (0.5)	88

[a] Under N_2.

When **1a** was treated with 0.5 equiv *p*-TsOH in benzene at 60 °C for 1 day under nitrogen atmosphere, the dimerization did not proceed at all (entry 12), indicating that the oxygen present in air serves as the oxidant to furnish pyrrolinone **2a**. Moreover, the reaction delivered pyrrolinone in a good yield even in the presence of an excess amount of a radical scavenger [(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)], indicating that this reaction possibly proceeds with the ionic mechanism (entry13). Furthermore, it was confirmed the reaction also proceeded in toluene without significant decrease of the yield of **2a** (entry 14).

Based on the abovementioned experimental facts, a plausible mechanism is illustrated in Scheme 3. First, the β-carbon of enamide **1a** attacks the α-carbon of another protonated enamide **A** to afford intermediate **B**. At this time, equimolar amounts of unprotonated and protonated enamides, **1a** and **A**, are necessary. The former maintains the nucleophilicity, and the latter improves the electrophilicity. After the elimination of an amine, the intramolecular cyclization affords a five-membered product **D**. Then, **D** is oxidized by molecular oxygen in the air,[13] and epoxide **F** is formed by dehydration.[14] The subsequent ring-opening reaction by water affords 1,2-diol **G**. Finally, the 1,2-migration of the methyl group[15] affords the final product 2-pyrrolin-4-one **2a**.

Other enamides **1a**–**e** were subjected to this dimerization using the optimized reaction conditions (Table 2). *N*-Unsubstituted enamides **1a**–**c** ($R^2 = R^3 = H$) efficiently afforded the corresponding pyrrolinones **2a**–**c** in excellent yields, respectively (entries 1–3). On the other hand, bulkiness on the amide function suppressed the dimerization, leading to pyrrolinones **2d** and **2e** in lower yields under the same conditions (entries 4 and 5). The obtained pyrrolinones **2a**–**e** could not be prepared by alternative procedures.

In conclusion, we have successfully developed a facile and efficient method for the synthesis of polysubstituted pyrrolinones by the dimerization of 3-amino-2-butenamides **1** by treating with 0.5 equiv *p*-TsOH under mild reaction conditions with simple manipulations. Moreover, the substituents at the 1-position of pyrrolinone **2** and the amide function can be easily modified by changing enamide **1**. This is advantageous for the construction of a new compound library. Only simple experimental manipulations are required, and this reaction proceeded without special reagents such as metal catalysts and oxidants. Hence, this reaction is expected to be a useful tool for the synthesis of versatile pyrrolinones.

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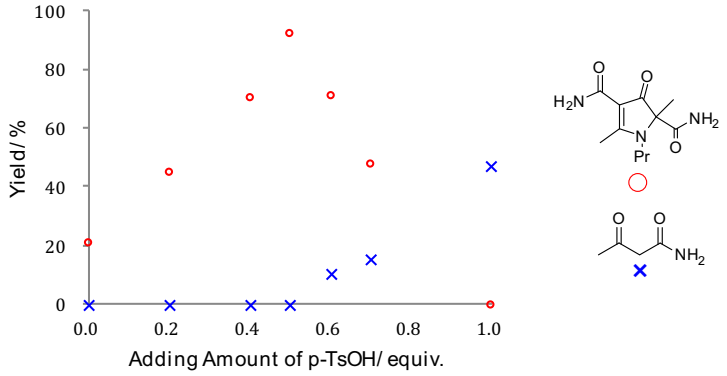
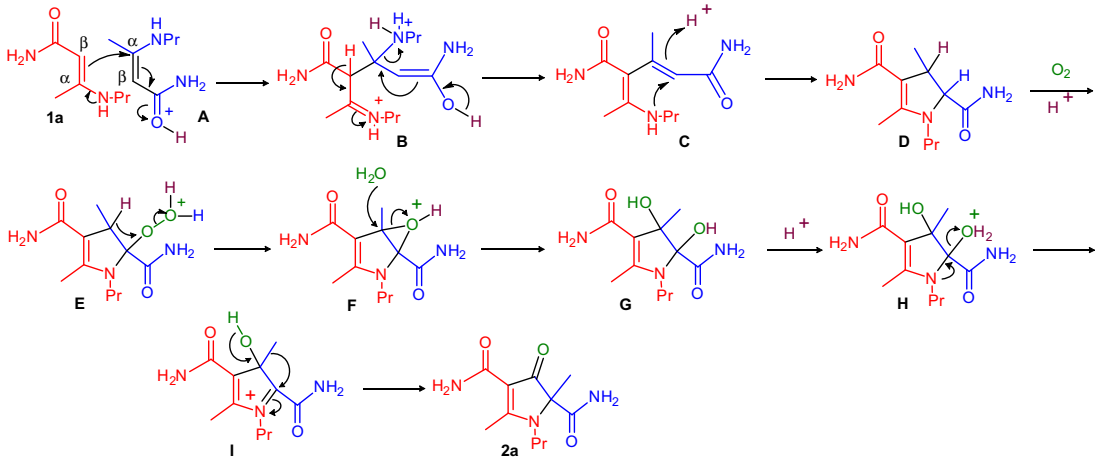
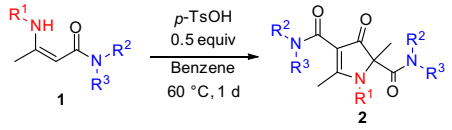


Fig. 2. The yield **2a** (○) and acetoacetamide (×) depending on the amount of *p*-TsOH.



Scheme 3. A plausible mechanism.

Table 2
Bicyclization of other substituted keto esters **1**.



Entry	R^1	R^2	R^3	Product	Yield (%)	Recovery (%)
1	Pr	H	H	**2a**	92	0
2	*i*-Bu	H	H	**2b**	96	0
3	$PhCH_2$	H	H	**2c**	93	0
4	Pr	Me	H	**2d**	35	31
5	Pr	Me	Me	**2e**	21	22

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.11.068.

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