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Efficient Synthesis of Highly Substituted Pyrrolin-4-ones via PIFA-Mediated Cyclization Reactions of Enaminones

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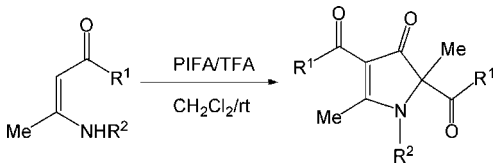
ABSTRACT



A convenient and efficient synthesis of highly substituted pyrrolin-4-ones is developed via the PIFA-mediated cyclization reactions of readily available enaminones, and a mechanism involving sequential cleavage of N–C bond, formation of new N–C bond, intramolecular addition reaction, and benzilic acid type rearrangement is proposed.

Due to their promising structural feature, enaminones have emerged as versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.[1,2] Their chemistry has been the focus of intense research for decades, particularly in heterocyclic synthesis, and continues to be an active area of research today.

On the other hand, hypervalent iodine reagents have been extensively used as the oxidation reagents in synthetic organic chemistry.[3] One such reagent, phenyliodine(III) bis-(trifluoroacetate) (PIFA) has attracted considerable attention recently due to its ready availability, low toxicity, easy handling, and reactivity similar to that of heavy metal reagents.[4] Its efficient utilization in the metal-free transformations relies on both the extremely mild reaction conditions required and its ability to oxidize chemoselectively a wide range of functionalities such as phenols, amines, sulfides, and carbonyl compounds. Recently, Tellitu and co-workers developed novel metal-free approaches to the synthesis of nitrogen-containing heterocycles using properly substituted amides and amines as synthetic precursors in which an intramolecular N−N, N−S, or N−C bond is formed through a PIFA-mediated oxidization process.[5]

During the course of our studies on β-oxo amide derivatives in the synthesis of carbo- and heterocycles,[6] we successfully developed an efficient one-pot synthesis of substituted isothiazol-3(2*H*)-ones from readily available α-carbamoyl ketene (*S*,*S*)-acetals in the presence of PIFA.[7] Thus, in connection with this previous work and following

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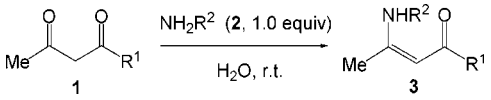
on from our research on the synthesis of highly valuable heterocycles through oxidative processes, we have prepared a series of enaminones from 1,3-dicarbonyl compounds and examined their reactivity toward the environmentally friendly reagent PIFA. As a result of these studies, we have developed a simple and efficient synthesis of highly substituted pyrrolin-4-ones via the PIFA-mediated cyclization of readily available enaminones.

Pyrrolin-4-one derivatives are an important class of functionalized nitrogen-containing heterocycles along with useful biological activities and widely used as key building block for the development of anticancer, antithrombotic, and antimicrobial agents.[8] Smith and Hirschmann have defined a pyrrolin-4-one-based scaffold that mimics peptide β-sheet backbone hydrogen-bonding donors, acceptors, and side chains[9] and extended that to the design of substrate mimetics of HIV-1 protease[10] and ligands of MHC class II proteins.[11] So far, extensive research has generated many procedures for the synthesis of pyrrolin-4-ones, such as formal [2 + 3] cycloaddition reaction of cyclopropenones with imine derivatives containing the C═N moiety,[12] cyclocondensation reactions of α-amino ester derivatives with aldehydes[13] and vicinal tricarbonyls with enamines or amines,[14] intramolecular cyclization of 2-azabutadienes,[15] and intramolecular alkylation reaction of 3-hydroxy pyrroles.[16] In the present paper, we provide a novel and alternative access route to substituted pyrrolin-4-ones through a PIFA-mediated oxidative cyclization.

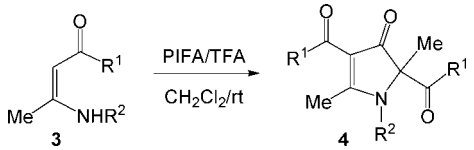
Substrate enaminones **3** were prepared from 1,3-dicarbonyl compounds **1** with various amines **2** in very high yields according to the reported procedure (Scheme 1).[17] We

Scheme 1. Preparation of Substrates Enaminones **3**



selected 3-(benzylamino)-*N*-phenylbut-2-enamide **3a** from a series of substrates **3**, see Table 1, as the model compound to examine its behavior under different conditions.

Table 1. The Cyclization Reactions of Enaminones **3**[a]



entry	**3**	R^1	R^2	time (h)	**4**	yield[c] (%)
1	**3a**	PhNH	Bn	4.5	**4a**	65
2	**3b**	4-MePhNH	Bn	5.0	**4b**	60
3	**3c**	4-MeOPhNH	Bn	4.0	**4c**	61
4	**3d**	4-ClPhNH	Bn	5.0	**4d**	59
5	**3e**	2-MePhNH	Bn	4.0	**4e**	64
6	**3f**	2-MeOPhNH	Bn	4.5	**4f**	58
7	**3g**	2-ClPhNH	Bn	5.0	**4g**	62
8	**3h**	PhNH	Me	4.0	**4h**	68
9	**3i**	4-MePhNH	Me	4.0	**4i**	65
10	**3j**	4-MeOPhNH	Me	4.0	**4j**	69
11	**3k**	4-ClPhNH	Me	4.5	**4k**	75
12	**3l**	2-MePhNH	Me	4.0	**4l**	63
13	**3m**	2-MeOPhNH	Me	4.0	**4m**	61
14	**3n**	2-ClPhNH	Me	4.5	**4n**	66
15	**3o**	PhNH	Ph	4.0	**4o**	77
16	**3p**	2-MePhNH	Ph	4.5	**4p**	71
17[b]	**3q**	OEt	Bn	3.0	**4q**	68
18[b]	**3r**	OEt	Me	2.5	**4r**	59
19	**3s**	Me	Bn	3.5	**4s**	23 (52)[d]
20	**3t**	Me	Me	3.0	**4t**	0 (67)[d]

[a] Reagents and conditions: **3** (1.0 mmol), PIFA (1.0 mmol), TFA (2.0 mmol), CH_2Cl_2 (100 mL), rt. [b] The concentration of PIFA is 0.1 M. [c] Isolated yields. [d] The data in parentheses is for compounds **5**.

Upon treatment of **3a** with PIFA (1.0 equiv, 0.05 M) and trifluoroacetic acid (TFA, 3.0 equiv) in CH_2Cl_2 at room temperature for 4.5 h, the reaction furnished a product after

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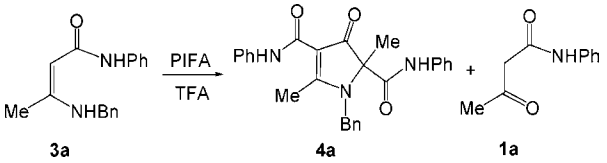
workup and purification (column chromatography) of the resulting mixture, which was characterized as a substituted pyrrolin-4-one **4a** (57% yield) on the basis of its spectral and analytical data (Scheme 2). Meanwhile, compound **1a**, the precursor of **3a**, was obtained as a byproduct in 21% yield. The structure of **4a** was further confirmed by the X-ray single-crystal analysis (Figure 1).

Scheme 2. Reaction of Enaminone **3a** in the Presence of PIFA/TFA



3a 4a 1a

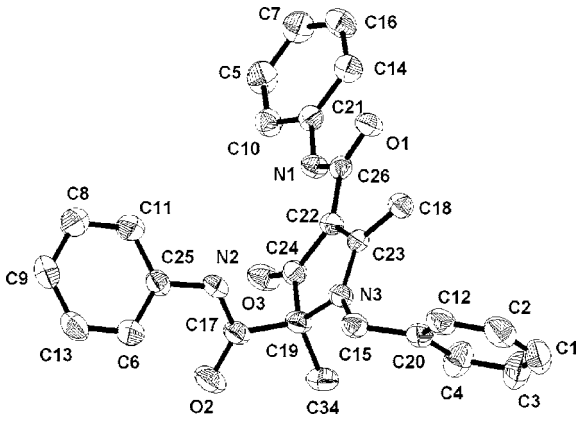


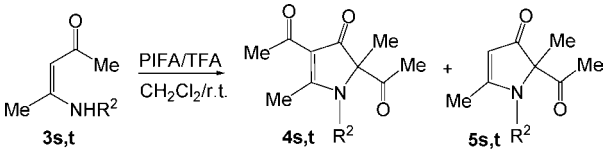
Figure 1. ORTEP drawing of **4a**.

The optimization of the reaction conditions, including reaction temperature, solvents, concentration of PIFA, and feed ratio of PIFA, TFA, and **3a**, were then investigated. Variation of the reaction temperature in the range 0−40 °C has no significant influence on the reaction. The reaction also proceeds in other polar solvents, such as DMF, THF, and acetonitrile, although CH_2Cl_2 proved to be the most efficient medium for the cyclization reaction. The concentration of PIFA plays an important role in the reaction. A high concentration of PIFA, more than 0.1 M, for example, results in a low yield. In the absence of TFA, the reaction proceeded sluggishly, and as indicated by TLC compound **1a** was formed and accumulated. A series of experiments revealed that the optimal results were obtained when the reaction of **3a** was performed with PIFA (1.0 equiv, 0.01 M) in CH_2Cl_2 at room temperature in the presence of TFA (2.0 equiv), whereby the yield of **4a** reached 65% (Table 1, entry 1).

Having established the optimal conditions for the key cyclization process, we aimed to determine its scope with respect to the amide moiety and amine functionality of substrates **3**. Thus, a series of enaminones **3b**−**p** were subjected to PIFA/TFA under the optimized conditions. As shown in Table 1 (entries 2−7), the PIFA-mediated cyclization reaction proved to be suitable for **3b**−**g** with varied aryl amide groups, affording the corresponding substituted pyrrolin-4-ones **4b**−**g** in moderate to good yields. The versatility of this pyrrolin-4-one synthesis was further evaluated by performing **3h**−**p** bearing methylamino or phenylamino groups under the identical conditions (entries 8−16). The results shown above demonstrate the efficiency and synthetic value of the cyclization reaction of variable enaminones **3**. It should be noted that the richness of the functionality of substituted pyrrolin-4-ones **4** may render them versatile as synthons in further synthetic transformations, for example, upon hydrogenation to their pyrrolidinone and pyrrolidine analogues.[18]

It is worth mentioning that in Tellitu's recent work on a novel N−N bond formation for the synthesis of indazol-3-ones, the key cyclization step is assumed to involve the formation of an *N*-acylnitrenium ion,[19] mediated by PIFA, and its subsequent intramolecular trapping by the amine moiety.[5d] In contrast, our results suggested that a nitrenium ion was generated at alkylamino group of substrate **3** instead of aryl amide moiety. These findings encouraged us to extend the scope of the cyclization protocol to other types of enaminones. Thus, we examined the reactions of enaminones **3q** and **3r**, prepared from *β*-oxo esters, under the same conditions. Unfortunately, it was found that the reactions proceeded sluggishly with much lower conversions and yields. However, with increase of the concentration of PIFA to 0.1 M, the reactions could afford the corresponding pyrrolin-4-ones **4** in good yields (entries 17 and 18). Interestingly, when subjecting **3s**, prepared from acetylacetone, to the identical conditions as for **4a**, the reaction furnished two products, which were characterized as pyrrolin-4-ones **4s** (23%) and **5s** (52%) on the basis of their spectra and analytical data (entry 19, Scheme 3). Apparently,

Scheme 3. Reactions of Enaminones **3s**/**3t**



3s,t 4s,t 5s,t

compound **5s** is formed by the deacylation of the corresponding **4s** under the acidic conditions. As indicated by

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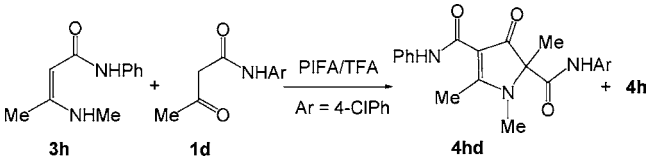
TLC, **4s** could be converted completely into **5s** by further stirring (8.0 h) at room temperature. In the case of **3t**, only the corresponding deacylation product **5t** was obtained in 67% yield (entry 20, Scheme 3).

Further experiments were conducted in order to gain insight into the mechanism of the cyclization reaction. In the absence of PIFA, the reaction of **3h** with 2.0 equiv of TFA was performed at room temperature for 30 min and then quenched with saturated aqueous $NaHCO_3$. Compound **1h** was obtained in 93% yield. This result implied that the above cyclization reaction of **3** might take place between compounds **3** and **1** instead of two molecules of compound **3**. Thus, we examined the reaction of **3h** and **1d** under the same conditions as for **4h** in Table 1. After workup and purification, to our delight, compounds **4hd** and **4h** were obtained in 19% and 43% yields, respectively (Scheme 4).

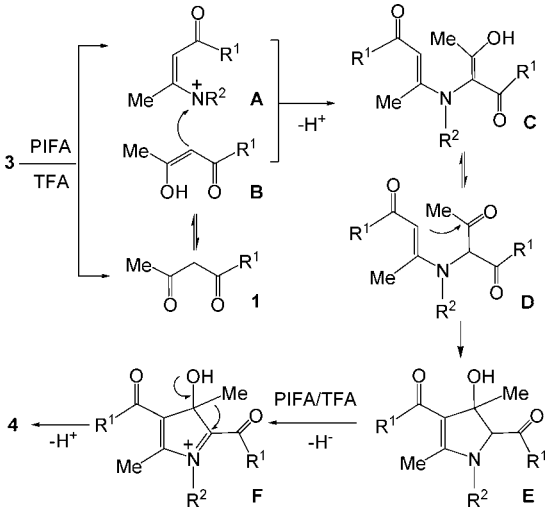
Scheme 4. Reaction between **3h** and **1d**



The structure of compound **4hd** was confirmed by its elemental analyses and NMR spectra in comparison to that of **4h** and **4k**. The mass spectra of **4hd** (398.1 $[M + 1]^+$) are consistent with the NMR results. All of the results reveal that TFA is a useful additive assisting the cleavage of enaminone **3** and provides the acidic conditions promoting the novel cyclization to **4**.

A plausible mechanism for the synthesis of substituted pyrrolinones **4** based on the results obtained is presented in Scheme 5. The overall transformation commences from the cleavage of enaminone **3** (at least 0.5 equiv) in the presence of TFA yielding **1**, and the simultaneous formation of nitrenium ion **A** generated from **3** (less than 0.5 equiv) by the action of the mild oxidant PIFA. The nitrenium ion **A** reacts with **B**, the tautomer of **1**, to give intermediates **C** and **D**. Then an intramolecular addition reaction of **D** via the enamine chemistry occurs under acidic conditions to give **E**, followed by a PIFA-mediated oxidation to form iminium

Scheme 5. Proposed Mechanism of the Cyclization of **3**



ion **F**, which finally undergoes a benzilic acid type rearrangement affording the product **4**.[14a,20] If R^1 of **4** is a methyl group, a deacylation reaction of **4** easily takes place to give the corresponding pyrrolin-4-one of type **5**.

In summary, a convenient and efficient synthesis of highly substituted pyrrolin-4-ones **4** is developed via the PIFA-mediated cyclization reactions of readily available enaminones **3**, which involves sequential cleavage of N−C bond, new N−C bond formation, intramolecular C−C bond formation, and benzilic acid type rearrangement processes. This protocol is associated with readily available starting materials, mild conditions, good yields, and broad range of synthetic potential of the products. Further work on the scope of the cyclization protocol and its application is currently underway in our laboratory.

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Supporting Information Available: Experimental details, spectral data, and copies of ^1H NMR and ^{13}C NMR spectra for compounds **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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