ORGANIC LETTERS

2010
Vol. 12, No. 17
3918−3921

Highly Efficient and Expedient Synthesis of 5-Hydroxy-1*H*-pyrrol-2-(5*H*)-ones from $FeCl_3$-Catalyzed Tandem Intramolecular Enaminic Addition of Tertiary Enamides to Ketones and 1,3-Hydroxy Rearrangement

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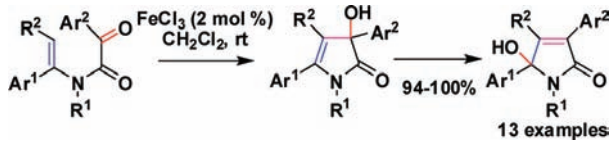
Received July 12, 2010

ABSTRACT



Catalyzed by $FeCl_3$ under very mild conditions, tertiary enamides underwent a highly efficient intramolecular enaminic addition reaction to the ketonic carbonyls followed by 1,3-hydroxy rearrangement to produce 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones in excellent yields.

5-Hydroxy-1*H*-pyrrol-2(5*H*)-ones **1** are important N-heterocyclic compounds in organic chemistry. Not only is the heterocyclic structure found in natural products such as oteromycin,[1] a microbial metabolite acting as an antagonist of endothelin receptor, but also some synthetic 5-hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives have been shown to possess interesting pharmacological properties[2] and neuritogenic activity.[3] In addition, 5-hydroxy-1*H*-2(5*H*)-ones are useful intermediates in synthesis.[4−6] For example, 5-allyl-5-hydroxy-3-iodo-1*H*-pyrrol-2(5*H*)-one has been used as a key intermediate in the total synthesis of natural product lucilactaene, a cell cycle inhibitor active in p53-inactive cells.[4] A few synthetic approaches to 5-hydroxy-1*H*-pyrrol-2(5*H*)-one skeletons have been reported in the literature (Figure 1). They mainly include: (1) the condensation reaction between α,*β*-diketones with acetamides bearing a strong electron-withdrawing group in the α-position;[3,7] (2) selective reduction of maleimide derivatives[6,8] and addition of an organometallic agent to

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10.1021/ol101607z
Published on Web 08/10/2010

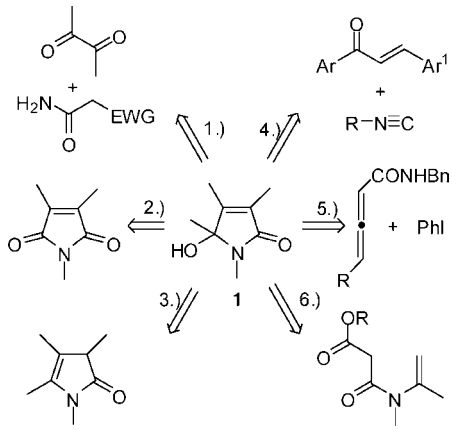

Figure 1. Reported synthetic approaches to 5-hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives.

maleimide derivatives;[4] (3) oxidation of pyrrolinones;[5,9] (4) reaction of isonitriles with chalcones;[10] (5) a Pd(0)-catalyzed coupling reaction of 2,3-allenamides with aryl iodide;[11] and (6) ceric ammonium nitrate (CAN) mediated oxidative 5-*endo*-cyclization of enamides.[12] These methods however suffer from drawbacks such as low chemical yield, poor regioselectivity, or substrate limitations. The development of new synthetic methods is therefore highly desirable.

Enamines[13] are very useful intermediates in organic synthesis.[14] The importance of enamine chemistry has been illuminated recently by asymmetric organocatalysis using chiral amine derivatives.[15] As the enamine variant, enamides are, however, stable and show diminished nucleophilic reactivity because of the electron-withdrawing effect of the *N*-acyl group which alleviates the delocalization of the lone-pair electrons on nitrogen into the carbon−carbon double bond.[16] The stability of enamides has been exemplified by the observation of many enamide natural products.[17] The majority of the synthetic application of enamides is their catalytic hydrogenation reactions for the preparation of enantioenriched α-amino acid derivatives.[18] In recent years, Kobayashi[19] has shown that secondary enamides, the enamide species bearing an N−H moiety (Figure 2), are able

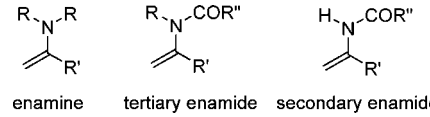

Figure 2. Enamine, tertiary enamide, and secondary enamide.

to react with different electron-deficient reactants in the presence of a Lewis acid catalyst. These secondary enamides behave actually as the aza-ene components to undergo the aza-ene reactions.[19,20] The enaminic (nucleophilic) reactions of tertiary enamides (Figure 2) are very rare.[16,21] Only very strong electrophiles such as acid chlorides, acid anhydrides, and iminium salts (the Vilsmeier reagent) are reported to react with tertiary enamides or enecarbamates.[21] In the study of the synthesis of clausena alkaloids, however, we[22] found that tertiary enamides can act as good nucleophiles to react with epoxide to form homoclausenamide alkaloids. This led us to explore the enaminic reactions of enamides. We envisioned that the ready availability of various enamides[23] and their good stability would render enamides as valuable and unique nucleophilic reagents in organic synthesis. We report herein highly efficient $FeCl_3$-catalyzed intramolecular nucleophilic addition of enamides to ketones followed by 1,3-hydroxy shift reaction. The reaction provided a very convenient and expedient access to 5-hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives in excellent yields.

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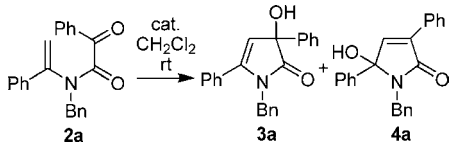
We started our study with a catalytic reaction of enamide **2a** which was obtained readily from the reaction of imine with 2-oxo-2-phenylacetyl chloride (see Supporting Information). Having considered the natural abundance, cost, environmental impact, and convenience of handling, Lewis acids derived from zinc, copper, and iron were chosen as catalysts (Table 1). In the presence of a catalytic amount of $ZnCl_2$ (10 mol %), enamide **2a** was found to undergo reaction smoothly at room temperature. After about two days, 1-benzyl-3-hydroxy-3,5-diphenyl-1*H*-pyrrol-2(3*H*)-one **3a**, the product resulting from direct intramolecular nucleophilic addition of enamide to ketone carbonyl, was obtained in 53% yield. Surprisingly, the reaction also produced a moderate yield of 1-benzyl-5-hydroxy-3,5-diphenyl-1*H*-pyrrol-2(5*H*)-one **4a** (entry 1, Table 1). The use of $Zn(OTf)_2$ as a catalyst gave a similar result but with a slight preference for the formation of product **4a** (entry 2, Table 1). While $[Cu(CH_3CN)_4]PF_6$-catalyzed reaction proceeded slowly to afford a mixture of products **3a** (54%) and **4a** (26%) (entry 3, Table 1), $Cu(OTf)_2$ was able to catalyze the reaction of **2a** efficiently to produce **4a** as the sole product in almost quantitative yield (entry 4, Table 1). Both $AlCl_3$ and $Sn(OTf)_2$ were effective catalysts for the transformation of **2a** into **4a**, albeit the former catalyst was less active than the latter (entries 5 and 6, Table 1). To our delight, $FeCl_3$ was found to be a very active Lewis acid catalyst. It catalyzed the reaction of enamide **2a** very rapidly to give quantitative yield of product **4a** (entry 7, Table 1). $FeCl_3{\cdot}6H_2O$ also catalyzed the reaction but with diminished efficiency (entry 8, Table 1). It is noteworthy that transformation of **2a** into **4a** proceeded equally efficiently with the use of a decreased catalyst loading (entry 9, Table 1), and rapid and quantitative conversion of **2a** into **4a** was achieved even with the use of 0.5 mol % of catalyst (entry 10, Table 1). The efficient $FeCl_3$-catalyzed reaction also took place in other solvents such as $CHCl_3$ (entry 11, Table 1) and toluene (entry 12, Table 1). However, a polar solvent such as acetonitrile slowed down the transformation of **2a** (entry 13, Table 1), whereas methanol completely inhibited the reaction (entry 14, Table 1). It should be addressed that compound **3a** was the precursor of product **4a**, as the treatment of isolated **3a** with a catalytic amount of $FeCl_3$ (2 mol %) in CH_2Cl_2 at room temperature led to the exclusive formation of **4a**.

Table 1. Optimization of Catalytic Reaction of Enamide **1a**[a]



entry	cat. (mol %)	solvent	time	**3a** (%)[b]	**4a** (%)[b]
1	$ZnCl_2$ (10)	CH_2Cl_2	47 h	53	34
2	$Zn(OTf)_2$ (10)	CH_2Cl_2	47.5 h	22	48
3	$[Cu(CH_3CN)_4]PF_6$ (10)	CH_2Cl_2	46.5 h	54	26
4	$Cu(OTf)_2$ (10)	CH_2Cl_2	5 h	–	98
5	$AlCl_3$ (10)	CH_2Cl_2	60 h	–	97
6	$Sn(OTf)_2$ (10)	CH_2Cl_2	20 min	–	95
7	$FeCl_3$ (10)	CH_2Cl_2	15 min	–	99
8	$FeCl_3{\cdot}6H_2O$ (10)	CH_2Cl_2	2 h	–	98
9	$FeCl_3$ (2)	CH_2Cl_2	15 min	–	100
10	$FeCl_3$ (0.5)	CH_2Cl_2	20 min	–	100
11	$FeCl_3$ (2)	$CHCl_3$	15 min	–	100
12	$FeCl_3$ (2)	toluene	30 min	–	100
13	$FeCl_3$ (2)	CH_3CN	6 days	–	100
14	$FeCl_3$ (2)	CH_3OH	7 days	–	–

[a] A mixture of reactant **2a** (0.3 mmol) and catalyst in dry solvent (15 mL) was stirred at room temperature. The reaction was stopped when reactant was consumed. [b] Isolated yield.

The structures of **3a** and **4a** were established on the basis of spectroscopic data and elemental analysis. It should be noted that that the vinyl proton of **3a** gave its resonance peak at 5.58 ppm, while compound **4a** showed its vinyl proton signal at 7.01 ppm in their ^1H NMR spectra. The huge difference in chemical shift ($\Delta\delta = 1.43$ ppm) between two proton signals in ^1H NMR spectra reflected different structural features of two compounds. In the case of **3a**, because of the delocalization of nitrogen lone pair electrons into the carbon−carbon double bond, the electron density of C-3 was increased, leading to a shielding effect on the vinyl proton. On the contrary, the α,β-unsaturated system in compound **4a** resulted in the decrease of electron density of C-3, causing its vinyl proton signal to be downfield shifted. This difference was actually used as a diagnostic tool to differentiate these two products. To prove the structures beyond doubt, compound **3a** was converted into its O-methylated derivative **5** (Scheme S1, Supporting Information (SI)), and single-crystal molecular structures of **4a** and **5** were determined unambiguously by X-ray crystallography (Figure S1, SI).

Under the optimized reaction conditions, the scope of the reaction was explored. As indicated by the results in Table 2, all enamides tested underwent highly efficient intramolecular reaction to give 5-hydroxy-3,5-diaryl-1*H*-pyrrol-2(5*H*)-one products in excellent yields. The reaction was accelerated when ketone moiety was substituted by a 4-chlorophenyl group (entry 8, Table 2). The change of the substituent on nitrogen from benzyl (entries 1−9, Table 2) and allyl (entry 10, Table 2) to methyl and phenyl led to a decrease of reaction rate (entries 11 and 12, Table 2). It was noticeable that the stronger the nucleophilicity

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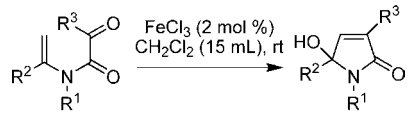
Table 2. $FeCl_3$-Catalyzed Reaction of Enamides **2**



2 **4**

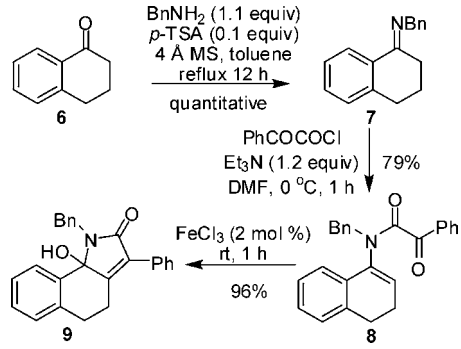
entry	**2**	R^1	R^2	R^3	t (min)	**4** (%)[a]
1	**2a**	Bn	Ph	Ph	15	**4a** (100)
2	**2b**	Bn	4-Me-C_6H_4	Ph	45	**4b** (100)
3	**2c**	Bn	4-Cl-C_6H_4	Ph	30	**4c** (96)
4	**2d**	Bn	4-Br-C_6H_4	Ph	40	**4d** (99.5)
6	**2e**	Bn	Ph	4-Me-C_6H_4	40	**4e** (100)
7	**2f**	Bn	Ph	4−F-C_6H_4	40	**4f** (99)
8	**2g**	Bn	Ph	4−Cl-C_6H_4	5	**4g** (98)
9	**2h**	PMB	Ph	Ph	30	**4h** (100)
10	**2i**	Allyl	Ph	Ph	30	**4i** (99)
11	**2j**	Me	Ph	Ph	120	**4j** (94)
12	**2k**	Ph	Ph	Ph	60	**4k** (94)

[a] Isolated yield.

of enamide and electrophilicity of the carbonyl, the faster the reaction.

The method was also applicable to other substrates. Scheme 1 illustrates, for example, the synthesis of a tricyclic

Scheme 1. Synthesis of Tricyclic Compound **9**

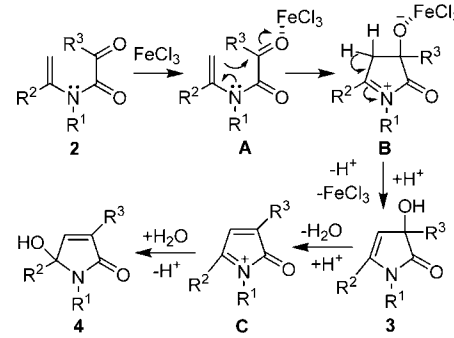


6 **7** **8** **9**

compound with the $FeCl_3$-catalyzed cyclization reaction as a key step. Thus, reaction of α-tetralone **6** with benzylamine gave a quantitative yield of imine **7** that underwent N-acylation using 2-oxo-2-phenylacetyl chloride to afford enamide **8** in 79%. $FeCl_3$-catalyzed reaction of enamide **8** produced 1-benzyl-9b-hydroxy-3-phenyl-4,5-dihydro-1*H*-benzo[*g*]indol-2(9b*H*)-one **9** in a very high yield (Scheme 1).

The $FeCl_3$-catalyzed intramolecular reaction of enamides **2** proceeded most probably through the direct enaminic (nucleophilic) reaction of enamide to the Lewis acid-activated ketone carbonyl to form a cyclic iminium intermediate **B**. Deprotonation of iminium afforded 3-hydroxy-3,5-diaryl-1*H*-pyrrol-2(3*H*)-one product **3**. Dehydration of **3** led to the formation of 2-oxo-2*H*-pyrrolium intermediate **C** which reacted with a water molecule to furnish the final 5-hydroxy-3,5-diaryl-1*H*-pyrrol-2(5*H*)-one products **4** (Scheme 2). It

Scheme 2. Mechanism of $FeCl_3$-Catalyzed Reaction



2 **A** **B** **4** **C** **3**

should be addressed that the activation of ketone carbonyl occurred via a monocoordination fashion. The chelation of α-oxo amide to iron is not beneficial or responsible for the intramolecular enaminic reaction because the rigid geometry of the chelation structure does not bring the proximity of enaminic carbon to ketone carbonyl carbon. Polar solvents such as acetonitrile and methanol compete with substrate to interact with iron catalyst, leading to a very slow reaction. The driving force of the rearrangement of the hydroxy group from C-3 to C-5 was most likely due to the stability gained from the formation of the 2-oxo-2*H*-pyrrolium intermediate and of an α,β-conjugation system in the final products.

In summary, we have provided a highly efficient and expedient access to 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones. The synthesis involves $FeCl_3$-catalyzed intramolecular enaminic addition of tertiary enamides to a ketonic carbonyl followed by 1,3-hydroxy rearrangement. The study of reactions of tertiary enamides with various electrophiles is being actively pursued in this laboratory.

Acknowledgment. We thank NNSFC, MOST, and CAS for financial support.

Supporting Information Available: Synthesis and characterization of products, ^1H and ^{13}C NMR spectra, and X-ray structure of **4a** and **5** (cifs). This material is available free of charge via the Internet at http://pubs.acs.org.

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