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ARTICLE TYPE

N-heterocyclic carbene - Catalyzed Synthesis of Functionalized 3-hydroxypyrrolidinones via a domino Aza-Michael/Aldol Reaction

Yan-fang Zhu, Chun Cai*

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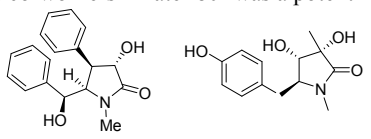
A practical and efficient synthesis of functionalized 3-hydroxypyrrolidinones through a domino Aza-Michael/Aldol reaction of α-ketoamides with chalcone has been realized. The domino reaction proceeded smoothly with NHC as a catalyst, affording 3-hydroxypyrrolidinones in good to excellent yields with excellent functional group tolerance.

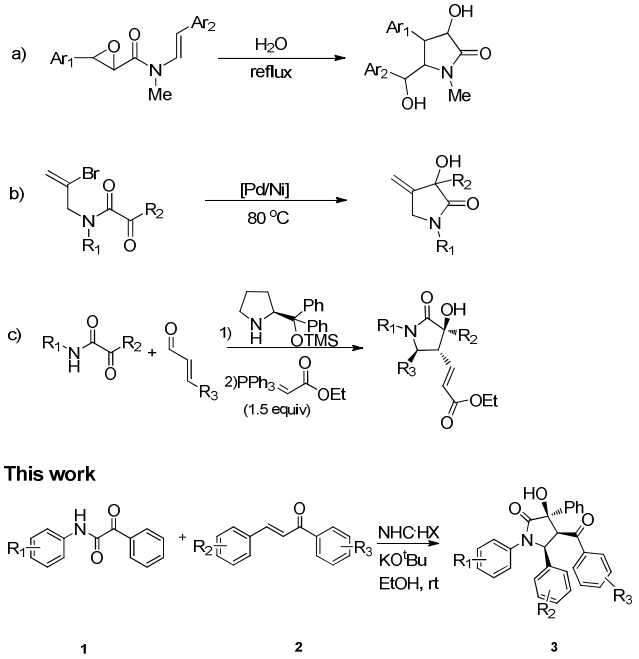
As one of the five-membered heterocyclic structural motifs, the substituted 3-hydroxypyrrolidinones are widely found in many pharmaceutically active compounds and natural products [1]. Many 3-hydroxypyrrolidinone-based pharmaceutical ingredients have exhibited potential therapeutical effect for many diseases such as depressive disorder, hepatitis, diabetes, cancers and so on [2]. For example, (-) - clausenamide (Fig 1) [3] which is a natural product isolated from the dried leaves of Clausena lansium (Lour.) Skeels by Huang and co-workers in later 80' was a potent nootropics [4].



(-)-Clausenamide Rigidiu sculamide A

Fig.1. Selected molecules containing 3-hydroxypyrrolidinone

Therefore, numerous efficient methods for the synthesis of 3-hydroxypyrrolidinone and their derivatives have been reported in the past. Among the broad variety of reactions developed, intramolecular enaminic reaction of enamide with the epoxide ring (scheme 1, route a) [5], nickel/palladium-catalyzed intramolecular addition of vinyl or aryl bromides to ketoamides (scheme 1, route b) [6-8] have been proven to be useful. However, these previously mentioned methods usually suffer from some disadvantages, such as the use of hazardous solvents, high reaction temperature, consisting of multiple steps, needing for a large amount of catalyst or transition metals as catalysts. Very recently, Enders and co-workers [9] presented a new convenient organocatalytic method for the synthesis of 3-hydroxypyrrolidinones via a domino Aza-Michael/Aldol reaction of α-ketoamides with α, β-unsaturated aldehydes using the catalyst diphenylprolinol trimethylsilyl ether (scheme 1, route c). Therefore, the development of mild synthetic methods of 3-hydroxypyrrolidinones with high stability is still in constant demand.



Scheme1. Synthesis of 3-hydroxypyrrolidinone derivatives

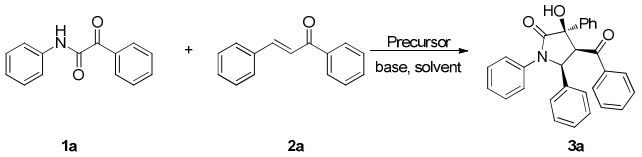
It is well-known that organocatalyzed domino reactions have developed into an important tool in synthetic chemistry during the past decade [10]. Domino reactions are typically atom-economical and can rapidly build up highly substituted compounds without the need for isolation of the intermediates. Among which, a number of small organic molecules have been used as catalysts in these reactions.

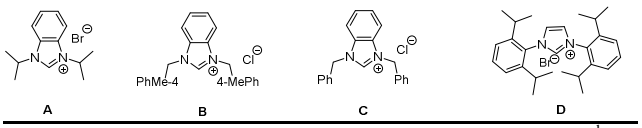
N-heterocyclic carbenes as an important and powerful class of organocatalysts also have been applied in domino reactions [11]. Furthermore, due to their strong basicity, some reports of aldol [12] and Michael reactions [13] catalyzed by NHCs have been developed. Building on these, we postulated that the effective organocatalyst NHC would allow this domino reaction to be conducted, resulting in a new methodology to produce stable 3-hydroxypyrrolidinones with α, β-unsaturated ketones and α-ketoamides (Scheme 1).

We first studied reaction of 2-oxo-N, 2-diphenylacetamide (**1a**) with chalcone (**2a**) by using KO^{t}Bu as a base (1.5 equiv) and carbene precursor **A** (10 mol%) in ethanol at room temperature. To our delight, the Michael/aldol domino reaction product **3a** was formed in 75% yield within 8 h (entry 1, Table 1). For optimization, the reaction was repeated under different conditions.

Different types of N-heterocyclic carbene precursors **A-D** were tested and **A** was found to be the most effective for the preparation of **3a** (Table 1, entries 1-4). According to several theoretical and experimental reports on the basicity of carbenes, [14] the basicity strength order may be **D** < **C** < **B**< **A**. The stronger basicity strengths of carbene exhibited better activity for this reaction (Table 1, entries 1-4). Notably, performing the reaction in the absence of NHC precursor led to a low yield product **3a** (entry 5, Table 1). With the amount of precatalyst **A** decreased to 5 mol%, the yield dropped to 44% and could not be improved even after prolonging the reaction time to 12 h (Table 1, entry 6). The base also plays a pivotal role in the reaction and we found that KO^{t}Bu gave the best yield of **3a** (Table 1, entry 1). Optimization of solvents for the synthesis of **3a** was also undertaken and it was found that among EtOH, MeOH and DMSO, the best solvent in terms of yield was EtOH (Table 1, entry 1). Finally, optimal amount of **1a** was selected. With the amount of **1a** increased to 1.3 equivalents, the yield could not be improved much more (Table 1, entry 15), so optimal amount of **1a** was selected to be 1.2 equivalents (Table 1, entry 1).

Table 1. NHC-Catalyzed optimization of conditions for the reaction of **1a** with **2a** [a]





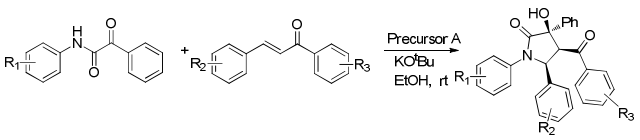
Entry	Precursor (mol%)	Base	**1a**:**2a**	Solvent	Yield [b] (%)
1	A(10)	KO^{t}Bu (1.5)	1.2:1	EtOH	75
2	B(10)	KO^{t}Bu (1.5)	1.2:1	EtOH	70
3	C(10)	KO^{t}Bu (1.5)	1.2:1	EtOH	66
4	D(10)	KO^{t}Bu (1.5)	1.2:1	EtOH	60
5	-	KO^{t}Bu (1.5)	1.2:1	EtOH	23
6 [c]	A(5)	KO^{t}Bu (1.5)	1.2:1	EtOH	44
7	A(10)	Na^{t}OBu (1.5)	1.2:1	EtOH	9
8	A(10)	KH_2PO_4 (1.5)	1.2:1	EtOH	-
9	A(10)	NEt_3 (1.5)	1.2:1	EtOH	34
10	A(10)	pyridine (1.5)	1.2:1	EtOH	32
11	A(10)	KOH (1.5)	1.2:1	EtOH	69
12	A(10)	K_2CO_3 (1.5)	1.2:1	EtOH	19
13	A(10)	KO^{t}Bu (1.5)	1.2:1	MeOH	54
14	A(10)	KO^{t}Bu (1.5)	1.2:1	DMSO	24
15	A(10)	KO^{t}Bu (1.5)	1.3:1	EtOH	76
16	A(10)	KO^{t}Bu (1.5)	1:1.2	EtOH	14

[a] Reaction conditions: **1a**, **2a** and NHC precursor were mixed together in solvent (2 ml) under N_2 and finally base was added, rt, 8 h. [b] Isolated yields . [c] reaction time is 12h.

Once the optimal conditions had been established, we proceeded to evaluate the generality of our method using a number of substituted α-ketoamides and α, β-unsaturated ketones (Table 2). As shown in Table 2, moderate to good yields (up to 78%) were obtained. Initially several structurally varied α, β-unsaturated ketone moieties **2** (Table 2) were used, employing the present optimized reaction conditions to afford the corresponding **3**. From the results obtained, it is clear that α, β-unsaturated ketones with electron-donating and electron-withdrawing groups at para-position or meta-position gave good yields of products (**3b, 3c, 3e-3i**). However, the steric hindrance at ortho-position of α, β-unsaturated ketones seems to have a desponding effect on yield. The ortho-position trifluoromethyl substituted α, β-unsaturated ketones gave the desired product in a lower yield than the corresponding chalcone (**3d**), because of the space steric effect. Furthermore, α-ketoamides with electron-donating or electron-withdrawing groups all furnished the desired products **3j** and **3k** in good yields.

Table 2. Reaction of α-ketoamides **1** with α, β-unsaturated ketones **2**

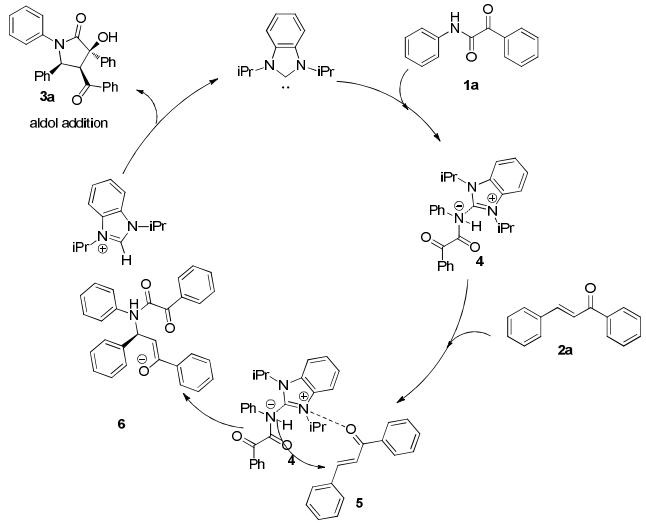
[a]



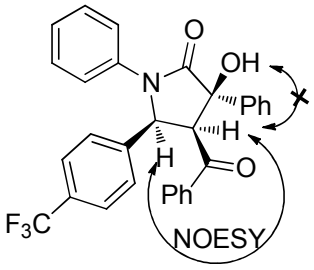
Entry	**1**	R^1	**2**	R^2	R^3	Product	Yield [b] (%)
1	**1a**	H	**2a**	H	H	**3a**	75
2	**1a**	H	**2b**	4-MeO	H	**3b**	69
3	**1a**	H	**2c**	4-Cl	H	**3c**	75
4	**1a**	H	**2d**	2-CF_3	H	**3d**	52
5	**1a**	H	**2e**	3-CF_3	H	**3e**	70
6	**1a**	H	**2f**	4-CF_3	H	**3f**	72
7	**1a**	H	**2g**	H	3- Cl	**3g**	64
8	**1a**	H	**2h**	H	4-Cl	**3h**	67
9	**1a**	H	**2i**	H	4-MeO	**3i**	71
10	**1b**	4-F	**2a**	H	H	**3j**	65
11	**1c**	4-MeO	**2a**	H	H	**3k**	78

[a] Reaction conditions: **1a** (0.36 mmol), **2a** (0.3 mmol) and precursor A (10 mol%) were mixed together in EtOH (2 ml) under N_2 and finally KO^{t}Bu (1.5 equiv) was added, rt, 8 h. [b] Isolated yields.

The mechanism of this reaction is speculated as shown in Scheme 2. N-heterocyclic carbene, generated from NHC salt upon treatment with base, reacts with α-ketoamides to form α-ketoamides-NHC complex **4**. This complex might activate α, β-unsaturated ketones and expedite the 1, 4-addition of α-ketoamides to α, β-unsaturated ketones, affording the acyclic intermediate **6**. The acyclic intermediate **6** that undergoes an aldol addition cyclization provides the product **3a** and regenerates the N-heterocyclic carbine (Scheme 2). The absolute configuration of the products was confirmed by NOESY experiment on **3f** (Scheme 3).



Scheme 2. Proposed mechanism



Scheme 3. Determination of the absolute configuration by NOESY measurement

In summary, we have identified an N-heterocyclic carbene as catalyst for aza-Michael/aldol domino reaction of α-ketoamides with α, β-unsaturated ketones to afford synthetically and pharmaceutically important 3-hydroxypyrrolidinone derivatives. The reaction features a transition-metal-free approach, mild reaction conditions, as well as a simple procedure. These features, together with the relative stability of the domino products, warrant the wide application of the current methodology for the synthesis of these 3-hydroxypyrrolidinones. Further investigation of the asymmetric synthesis of 3-hydroxypyrrolidinones catalyzed by chiral NHC is ongoing in our group.

Experimental Section

General Remarks

All of the reagents and solvents were commercially available and used without further purification. GC analyses were performed on an Agilent 7890A instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker DRX 500 and tetramethylsilane (TMS) was used as a reference. The ^{1}H NMR spectroscopic data of these precatalysts are in agreement with those reported in the literatures [13, 15-17]. The α-ketoamides were synthesized according to the literature [9].

General procedure for the Synthesis of 3-hydroxypyrrolidinones (3).

Under N_2 atmosphere, to a solution of catalyst precursor **A** (0.03 mmol), **1** (0.36 mmol) and **2** (0.3 mmol) in ethanol (2 mL) was added the KO^{t}Bu (0.45 mmol). The reaction was stirred at rt (monitored by TLC) before it was quenched with NH_4Cl (4mL, sat. aq.).The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography afforded 3-hydroxypyrrolidinones.

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Notes and references

[a] *Chemical Engineering College, Nanjing University of Science & Technology, 200 Xiaolingwei, Nanjing 210094, P. R. China. Fax: +86-25-84315030;Tel.: +86-25-84315514; E-mail: c.cai@mail.njust.edu.cn*

† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of products.

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