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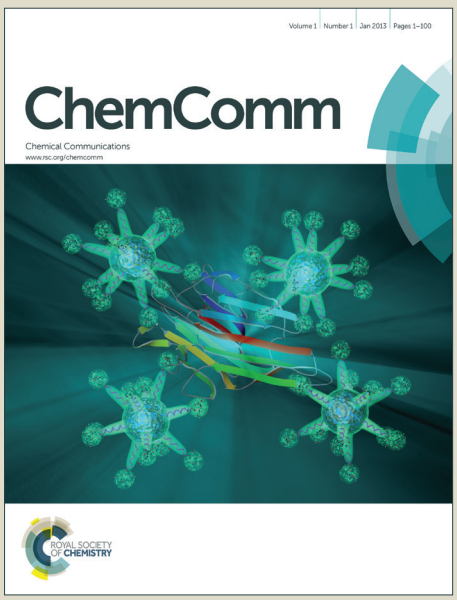

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ARTICLE TYPE

$ZnCl_2$-catalyzed Chemoselective Cascade Reactions of Enaminones with 2-Furylcarbinols: Versatile Process for the Synthesis of Cyclopenta[*b*]pyrrole Derivatives

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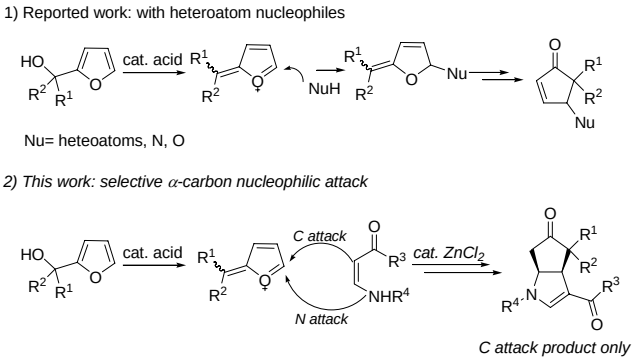
A highly efficient $ZnCl_2$-catalyzed cascade reaction of enaminones with 2-furylcarbinols under mild reaction conditions has been developed. This methodology offers chemo- and diastereo-selective access to functionalized cyclopenta[*b*]pyrrole derivatives in good to excellent yields.

Organic syntheses with chemoselectivity are of great value because it can avoid unnecessary protection and deprotection steps.[1] The selective reaction of a specific functional group in polyfunctional molecules is challenging. Enaminones are versatile building blocks in synthetic organic chemistry.[2] They combined the ambident nucleophilicity of enamines with the ambident electrophilicity of enones. Both α-carbon and amino group can be nucleophilic centers. Although much progress has been made in recent years in devising new process,[3] especially for heterocyclic synthesis,[4] on the utility of enaminones, the development of chemoselective reactions of enaminones for the precise construction of heterocyclic compounds with biological potential remains in high demand. On the other hand, 2-furylcarbinols are valuable synthetic precursors.[5] In 1970s, Piancatelli et al reported an interesting acid-catalyzed cascade rearrangement of certain 2-furylcarbinols for the synthesis of 4-hydroxycyclopentenone derivatives.[6] Since then much effort has been made for its application in the synthesis of biologically active products. Several elegant works have been disclosed recently based on Piancatelli rearrangement, such as intramolecular reactions with oxygen- or nitrogen-containing nucleophiles for the synthesis of oxa- or aza-spirocycles,[7] intermolecular reactions with amines to 4-substituted cyclopentenones [8] and others.[9] However, in all these reactions, only heteroatom nucleophiles were employed. There were no examples with carbon-nucleophiles, especially in an intermolecular fashion. Given the ambient properties of enaminone, we envisioned that the selective nucleophilic attack by the α-carbon of enaminone might be realized by proper choice of catalyst systems. During the course of our continued work on synthesis of heterocycles starting from enaminones,[10] we discovered novel cascade reactions of enaminones with 2-furylcarbinols divergently leading to the formation of



Scheme 1. The reaction of 2-furylcarbinols with nucleophiles

cyclopenta[*b*]pyrrole rings in good yields through chemoselective intermolecular α-carbon nucleophilic attacking/intramolecular Michael addition sequence. The resulting azabicyclic compounds are important azacarboprostacyclin analogs which are potentially useful in the treatment of thrombotic disease. [11]

Initial studies were conducted with furan-2-yldiphenylmethanol (**1a**) and enaminones **2**, which was readily prepared through conjugate addition of aniline to terminal alkynone.[11c] The reaction of **1a** with (*Z*)-1-phenyl-3-(phenylamino)prop-2-en-1-one (**2a**) was selected as a model case to screen the experimental conditions. Firstly, the reaction of **1a** with **2a** was carried out using CF_3COOH (10 mol%) as the catalyst in toluene at 80 °C, however, only trace amounts of the desired cyclopenta[*b*]pyrrole ring were detected (Table 1, entry 1). THF resulted in no formation of the target product (Table 1, entry 2). To our delight, when dichloroethane was used, the desired **3a** was produced in 66% yield (Table 1, entry 3). $TsOH{\cdot}H_2O$ gave 53% yield of the desired bicyclic compound (Table 1, entry 4). Lewis acids such as $Sc(OTf)_3$, $BF_3{\cdot}Et_2O$, $FeCl_3$ and $FeCl_3{\cdot}6H_2O$ gave good to high yields of the desired product, respectively (Table 1, entries 5-8). It is interesting that $ZnCl_2$ in DCE afforded **3a** in 94% yield within 2 h (Table 1, entry 9). Other solvents such as CH_3CN, toluene also produced the desired **3a** in good yields (Table 1, entries 10 and 11). 1,4-dioxane resulted in 42% of **3a** (Table 1, entry 12). However, THF or DMF gave no desired product (Table 1, entries 13 and 14). When the reaction was carried out at 50 °C in DCE, the desired product was obtained in 84% yield and required much longer reaction time (Table 1, entry 15). Reaction conducted at room temperature resulted in trace amount of **3a** even after 24 h (Table 1, entry 16).

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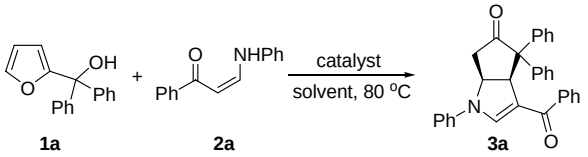
Lowering the catalyst loading to 5 mol% gave 89% yield of **3a** in 4 h (Table 1, entry 17). Changing the ratio of **1a**/**2a** resulted in slightly lower yields (Table 1, entries 18 and 19). A control experiment showed that no desired product was formed in the absence of $ZnCl_2$ (Table 1, entry 20). Therefore, the optimized reaction condition was to use 10 mol % of $ZnCl_2$ as the catalyst, and DCE as the solvent at 80 °C. One of the advantages of this method to prepare cyclopenta[*b*]pyrrole rings is that the cascade nucleophilic attack of the α-carbon of enaminone took place in a chemoselective manner to give only one isomer of the desired product (Scheme 1, eq. 2).

Table 1. Optimization of reaction conditions for the formation of **3a**



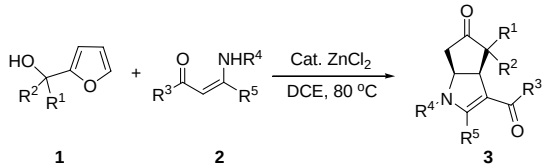
1a **2a** **3a**

entry	catalyst (mol%)	solvent	time(h)	yield(%)[a,b]
1	CF_3COOH (10)	Toluene	19	trace
2	CF_3COOH (10)	THF	3	--
3	CF_3COOH (10)	DCE	19	66
4	$TsOH{\cdot}H_2O$ (10)	DCE	19	53
5	$Sc(OTf)_3$ (10)	DCE	17	50
6	$BF_3{\cdot}Et_2O$ (10)	DCE	19	66
7	$FeCl_3$ (10)	DCE	5	68
8	$FeCl_3{\cdot}6H_2O$ (10)	DCE	5	81
9	$ZnCl_2$ (10)	DCE	2	94
10	$ZnCl_2$ (10)	CH_3CN	5	84
11	$ZnCl_2$ (10)	Toluene	2	86
12	$ZnCl_2$ (10)	1,4-dioxane	5	42
13	$ZnCl_2$ (10)	THF	5	--
14	$ZnCl_2$ (10)	DMF	2	--
15	$ZnCl_2$ (10)	DCE	6	84[c]
16	$ZnCl_2$ (10)	DCE	24	trace[d]
17	$ZnCl_2$ (5)	DCE	4	89
18	$ZnCl_2$ (10)	DCE	2	90[e]
19	$ZnCl_2$ (10)	DCE	2	92[f]
20	--	DCE	4	--

[a] Unless otherwise noted, all reactions were carried out in air in 0.25 mmol scale with the ratio of **1a** : **2a** = 1: 1. [b] Isolated yields. [c] The reaction was carried out at 50 °C. [d] The reaction was carried out at room temperature. [e] The ratio of **1a** : **2a** = 1: 1.2. [f] The ratio of **1a** : **2a** = 1.2: 1.

With the optimized reaction conditions in hand, we then examined the substrate scope of this cascade reaction for the synthesis of cyclopenta[*b*]pyrrole derivatives using a variety of enaminones and 2-furylcarbinols. The results are depicted in Table 2. We first investigated the electronic effects of the aromatic substituents on nitrogen of enaminones. It was found that an electron-withdrawing (-*p*-Cl) aryl group afforded the corresponding product **3b** in 78% yield (Table 2, entry 2). Electron-donating (-3,4,5-tri MeO, -2,6-di Me, 2,6-di ^{i}Pr) aryl groups also gave high yields of **3c**, **3d** and **3e**, respectively (Table 2, entries 3-5). The structure of **3c** was further confirmed as a *cis*-diastereomer by X-ray crystallographic analysis.[12] The substituents on nitrogen of enaminone could also be alkyl groups, such as benzyl (**2f**), *n*-hexyl (**2g**) and *t*-butyl (**2h**) with the corresponding **3f**, **3g** and **3h** obtained in 83, 65 and 90% yields with relatively longer reaction time, respectively (Table 2, entries 6-8). The electronic effects of the aromatic substituents on carbonyl carbon of enaminones were then examined. An electron-withdrawing (-*p*-Cl) aryl group gave **3i** in 82% yield (Table 2, entry 9), while an electron-donating (-3,4,5-tri MeO) aryl group produced **3j** in 87% yield (Table 2, entry 10). A naphthyl substituted enaminone was compatible under the reaction conditions, furnishing **3k** in 91% yield (Table 2, entry 11). The reaction also proceeded smoothly with cyclohexyl group (**2l**), affording the corresponding **3l** in quantitative yield (Table 2, entry 12). The cascade reaction has been successfully extended to enaminones with two substituents on the β-carbon. Enaminones

Table 2. Synthesis of various of cyclopenta[*b*]pyrrole rings



1 **2** **3**

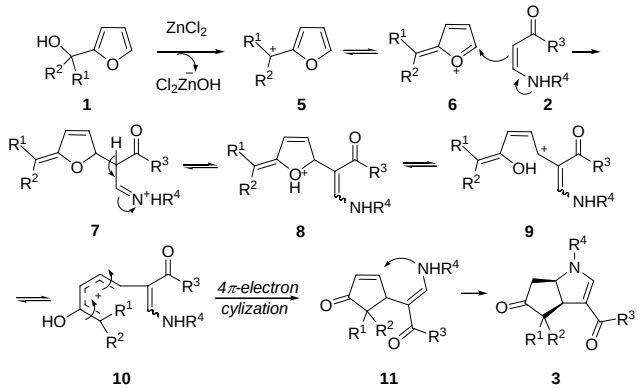
entry	**1** (R^1, R^2)	**2** (R^3/R^4/R^5)	time(h)	product	yield(%)[a]
1	**1a** (Ph, Ph)	**2a** (Ph/Ph/H)	2	**3a**	94
2	**1a**	**2b** (Ph/*p*-ClC_6H_4/H)	4	**3b**	78
3	**1a**	**2c** (Ph/*3,4,5-tri* $MeOC_6H_2$/H)	5	**3c**	93
4	**1a**	**2d** (Ph/*2,6-di* MeC_6H_3/H)	5	**3d**	85
5	**1a**	**2e** (Ph/*2,6-di* $^iPrC_6H_3$/H)	3	**3e**	92
6	**1a**	**2f** (Ph/Bn/H)	10	**3f**	83
7	**1a**	**2g** (Ph/^{n}Hex/H)	49	**3g**	65
8	**1a**	**2h** (Ph/^{t}Bu/H)	38	**3h**	90
9	**1a**	**2i** (*p*-ClC_6H_4/Ph/H)	3	**3i**	82
10	**1a**	**2j** (*3,4,5-tri* $MeOC_6H_2$/Ph/H)	3	**3j**	87
11	**1a**	**2k** (*1*-naphthyl/Ph/H)	3	**3k**	91
12	**1a**	**2l** (^{c}Hex/Ph/H)	4	**3l**	99
13	**1a**	**2m** (Ph/Ph/Ph)	48	**3m**	53
14	**1a**	**2n** (^{n}Bu/Ph/Ph)	14	**3n**	91
15	**1b** (*p*-ClC_6H_4,*p*-ClC_6H_4)	**2a**	7	**3o**	85
16	**1c** (*p*-ClC_6H_4,Ph)	**2a**	7	**3p**	72[b]
17	**1d** (^{n}Bu,Ph)	**2a**	4		-
18	**1e** (H,Ph)	**2a**	3		-

[a] Isolated yields. [b] d. r. = 1:1.2.

with one more phenyl group at the β-carbon, such as **2m** and **2n**, reacted with **1a** leading to the formation of **3m** and **3n** in 53 and 91% yields, respectively (Table 2, entries 13 and 14). It is noteworthy that the reaction time is much longer for these

substrates, presumably due to the steric hindrance. Other 2-furylcarbinols were also attempted in the cyclization reaction. Compound **1b** with two *p*-Cl aryl groups gave the corresponding bicycle **3o** in 85% yield (Table 2, entry 15). Incorporation of two different aryl groups on the 2-furylcarbinol in the reaction provided **3p** as two diastereomers in a good yield (Table 2, entry 16). Unfortunately, when furylcarbinol **1d** bearing an alkyl substituent was employed, no desired product was detected due to a competitive dehydration pathway. Furan-2-yl(phenyl)methanol (**1e**) with a secondary carbinol side chain reacted with **2a** resulting in no formation of the desired bicyclic compound.

On the basis of the above results and the reported work concerning the reaction of 2-furylcarbinols,[5,6] a possible reaction mechanism is proposed in Scheme 2. Initially, carbocation **5** or oxocarbenium ion **6** is generated in the presence of $ZnCl_2$, which is attacked by an α-carbon of enaminone **2** to give iminium **7**. Prototropic shift of **7** forms **8**. Acid-catalyzed rearrangement of **8** followed by the 4π-electrocyclization of **10** to produce cyclopentenone **11**. Intramolecular Michael addition leads to product **3**.



Scheme 2. A proposed reaction pathway

In order to 'observe' intermediate **11** before Michael addition, the reaction of **1a** with **2a** was carried out at lower temperature. However, no information about such intermediate could be obtained at the current stage. It seems that the intramolecular Michael addition step is fast.

In conclusion, we have shown that functionalized cyclopenta[*b*]pyrroles are efficiently prepared by the $ZnCl_2$-catalyzed cascade reactions using enaminones and 2-furylcarbinols. Aryl and alkyl substituents on enaminones are compatible in the cascade reactions, furnishing the desired cyclopenta[*b*]pyrrole derivatives in good to excellent yields. In this procedure, nucleophilic attack of the α-carbon of enaminones took place in a chemoselective manner followed by cascade Piancatelli rearrangement/Michael addition reactions to give only one *cis*-diastereomer of the desired bicyclic product.

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12 CCDC-966745 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.