Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

One-Pot Synthesis of Polysubstituted 3-Acylpyrroles Using Cooperative Catalysis

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

One-pot syntheses of polysubstituted 3-acylpyrroles from readily available unsaturated ketones and *N*-substituted propargylated amines have been developed. An aza-Michael/alkyne carbocyclization cascade, using cooperative catalysis by pyrrolidine and a copper salt, followed by oxidation in situ gave 3-acylpyrroles, which were also transformed further to functionalized, highly substituted 3-acylpyrroles.

Polysubstituted pyrroles and their unsaturated derivatives are structural motifs often found in natural products and pharmaceuticals.[1] In particular, 3-acylpyrroles are present in many drugs and biologically active compounds (Figure 1).[2] For example, molindone[2a] and piquindone[2a] are dopamine receptor antagonists and some Hsp90 inhibitors bearing the 3-acylpyrrole framework exhibit nanomolar antiproliferative activities across multiple cancer cell lines.[2b,c] The fact that all these compounds possess a 3-acylpyrrole moiety suggests that this framework may play an important role in the origins of the bioactivities, and molecules bearing the 3-acylpyrrole core have been synthesized for screening against a number of therapeutic agents.[1,2,3] Most of these 3-acylpyrroles have been synthesized from β-ketocarbonyl compounds or β-enaminones, imposing restrictions on diversity of the 3-acylpyrrole products.[2,3] The development of concise, efficient methods for the synthesis of 3-acylpyrroles and related heterocycles that allow access to a diverse set of these molecules from readily available starting materials remains a great challenge and has attracted much attention.[3]

Recently, cooperative catalysis that combines both nucleophile activation and electrophile activation using organocatalysts and metal catalysts has emerged to efficiently construct useful building blocks.[4,5] Our previous efforts to synthesize heterocyclic compounds based on amine-catalyzed C-C and C-O bond formation via an enamine/iminium cascade[6] led us to investigate the combination of amine-cascade catalysis and metal catalysis.

Inspired by recent achievements of the combination of transition-metal catalysis and organocatalysis,[4,5] we set out to synthesize highly substituted 3-acylpyrroles via the synergistic activation of enone and alkyne[7] to generate dihydropyrroles and by subsequent oxidation of the dihydropyrroles in one-pot (Figure 1).[8] This strategy may allow for the formation of C-N and C-C bonds to construct polysubstituted pyrroles with variation of substituents at all the five positions of the 3-acylpyrrole. For this strategy, however, there are also challenges to be addressed, such as poor activity of secondary amines in aza-Michael reactions,[9] discrimination between reactant amines and catalyst amines, and turnover of amine catalysts. Here, we disclose efficient methods to synthesize polysubstituted 3-acylpyrroles by cooperative catalysis from readily available unsaturated ketones and *N*-substituted propargylated amines using a secondary amine and a copper salt followed by oxidation in one-pot.

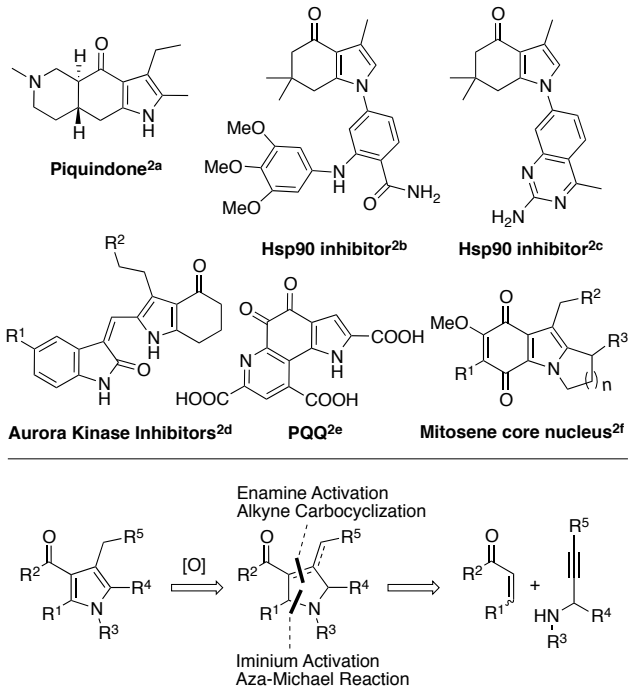


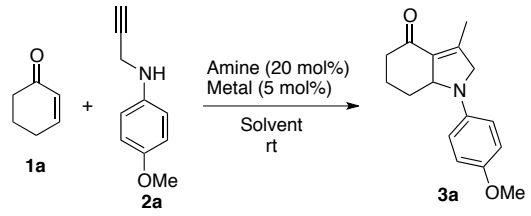
Figure 1. Pharmaceuticals and biologically active compounds bearing 3-acylpyrrole frameworks and one-pot route to the 3-acylpyrroles by cooperative catalysis.

To develop a general catalytic system for the synthesis of 3-acylpyrroles, first, the reaction of **1a** and **2a** to form **3a** in the presence of pyrrolidine and various metal catalysts was investigated (Table 1, entries 1-7). When the reaction was performed using $Cu(OTf)_2$ as the metal catalyst in the presence of PPh_3 to generate active species $Cu(PPh_3)_3OTf$,[5a] product **3a** was obtained in 75% yield (entry 6). Without PPh_3, no product formation was detected (entry 5).[10] CuI and the combination of AgOTf with PPh_3 showed comparable catalytic activities to the

$Cu(OTf)_2$ with PPh_3 (entries 4 and 7 versus entry 6). For Pd series, the reaction using $Pd(OAc)_2$ as the metal catalyst gave **3a** (entry 3), but $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ were not effective (entries 1 and 2).

Next, the reaction of **1a** and **2a** using the $Cu(OTf)_2$-PPh_3 system as the metal catalyst in the presence of amines other than pyrrolidine was evaluated (entries 8-12). In these reactions, formation of **3a** was very slow or negligible. Reaction in the presence of pyrrolidine alone without metal catalyst, in the presence of pyrrolidine and PPh_3 without metal catalyst, or in the presence of the $Cu(OTf)_2$-PPh_3 system without pyrrolidine also did not give **3a** (entries 13-15). These results clearly indicate that the combination of nucleophile activation and electrophile activation by pyrrolidine and the $Cu(PPh_3)_3OTf$ is crucial for the formation of the dihydropyrrole product.

Table 1. Screening of Catalysts and Conditions[a]

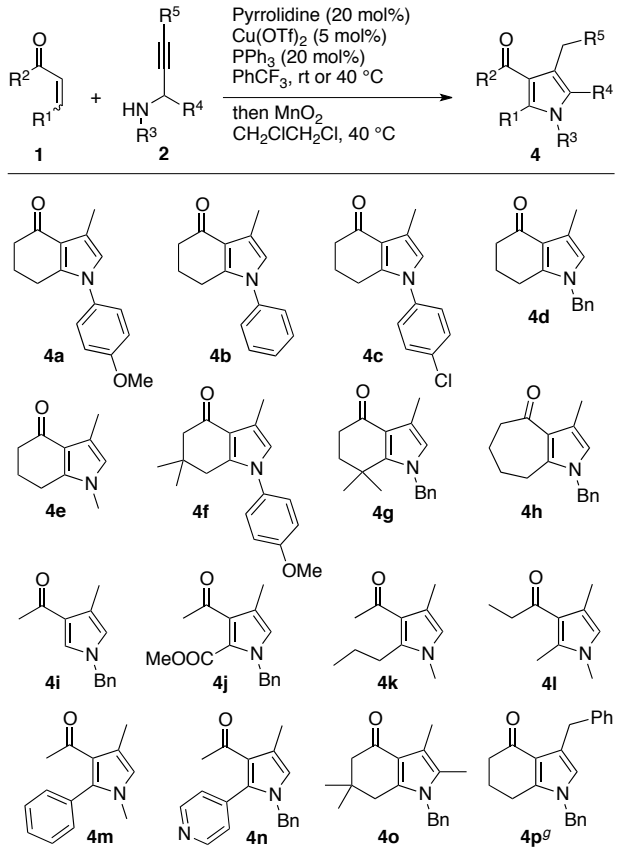


entry	metal	amine	solvent	time (h)	yield (%)[b]
1	$Pd(PPh_3)_4$	Pyrrolidine	CH_2Cl_2	50	7
2	$Pd(PPh_3)_2Cl_2$	Pyrrolidine	CH_2Cl_2	22	12
3	$Pd(OAc)_2$	Pyrrolidine	CH_2Cl_2	22	46
4	CuI	Pyrrolidine	CH_2Cl_2	22	54
5	$Cu(OTf)_2$	Pyrrolidine	CH_2Cl_2	25	ND
6[c]	$Cu(OTf)_2$	Pyrrolidine	CH_2Cl_2	17	75
7[c]	AgOTf	Pyrrolidine	CH_2Cl_2	17	63
8[c]	$Cu(OTf)_2$	Piperidine	CH_2Cl_2	47	26
9[c]	$Cu(OTf)_2$	Diethylamine	CH_2Cl_2	25	ND
10[c]	$Cu(OTf)_2$	Benzylamine	CH_2Cl_2	25	ND
11[c]	$Cu(OTf)_2$	Quinine	CH_2Cl_2	25	ND
12[c]	$Cu(OTf)_2$	DMAP	CH_2Cl_2	25	ND
13	-	Pyrrolidine	CH_2Cl_2	25	ND
14[c]	-	Pyrrolidine	CH_2Cl_2	25	ND
15[c]	$Cu(OTf)_2$	-	CH_2Cl_2	25	ND
16[c]	$Cu(OTf)_2$	Pyrrolidine	MeCN	48	60
17[c]	$Cu(OTf)_2$	Pyrrolidine	Toluene	25	61
18[c]	$Cu(OTf)_2$	Pyrrolidine	$PhCF_3$	22	91

[a] Reactions of **1** (0.2 mmol) and **2** (0.3 mmol) was performed using amine (0.04 mmol) and metal catalyst (0.01 mmol) in solvent (0.2 mL) at rt (25 °C). [b] Isolated yield of **3a**. ND = formation of **3a** was not detected. [c] PPh_3 (0.04 mmol) was added.

A solvent screening for the reaction using the $Cu(OTf)_2$-PPh_3-pyrrolidine catalyst system identified that $PhCF_3$ was the best solvent among those tested to afford **3a** in high yield (entries 16-18). Thus, the optimal results for the synthesis of dihydropyrrole **3a** were obtained under the reaction conditions using **1a** (1 equiv) and **2a** (1.5 equiv) in the presence of $Cu(OTf)_2$ (5 mol% to **1**), PPh_3, (20 mol%), and pyrrolidine (20 mol%) in $PhCF_3$ at room temperature (entry 18). [11]

Table 2. One-Pot Synthesis of 3-Acylpyrroles.[a]

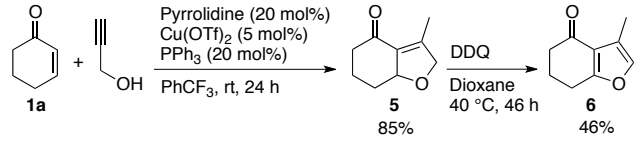


entry	product	first step temp	first step time (h)	oxidation step time (h)	yield (%)
1	**4a**	rt	23	5[b]	84
2[c]	**4a**	rt	51	68	66
3	**4b**	rt	45	44	69
4	**4c**	rt	67	31	55
5	**4d**	rt	24	24	84
6	**4e**	40 °C	22	66	59
7	**4f**	rt	24	25[b]	82
8[c]	**4f**	rt	54	50	81
9	**4g**	rt	20	43	71
10[c]	**4g**	rt	69	96[d]	61
11	**4h**	rt[e]	55	24	70
12	**4i**	rt	47	7	85
13	**4j**	rt	48	30	60
14	**4k**	40 °C	22	66	44
15	**4l**	40 °C[e]	52	42	20
16	**4m**	40 °C	20	46	47
17	**4n**	rt	49	25	60
18	**4o**	rt	24	38[f]	50

[a] Reaction of **1** (0.2 mmol) and **2** (0.3 mmol) was performed using pyrrolidine (0.04 mmol, 20 mol% to **1**), PPh_3 (0.04 mmol, 20 mol% to **1**), and $Cu(OTf)_2$ (0.01 mmol, 5 mol% to **1**) in $PhCF_3$ (0.2 mL, concentration of **1**: 1 M) at rt (25 °C). Upon consumption of **1**, MnO_2 (4.0 mmol) in CH_2ClCH_2Cl (2 mL) was added and the reaction mixture was stirred at 40 °C. [b] For the oxidation step, CH_2Cl_2 was used at rt instead of CH_2ClCH_2Cl at 40 °C. [c] 10 mmol scale (gram-scale) reaction; **1** (10 mmol) and **2** (12 mmol).[13] [d] 40 °C for 72 h and 60 °C for 24 h. [e] MeOH was used instead of $PhCF_3$ based on a screen of conditions (the reactions in $PhCF_3$ gave the product in lower yields). [f] Oxidation step at 50 °C. [g] Formation of **4p** was not detected; see text.

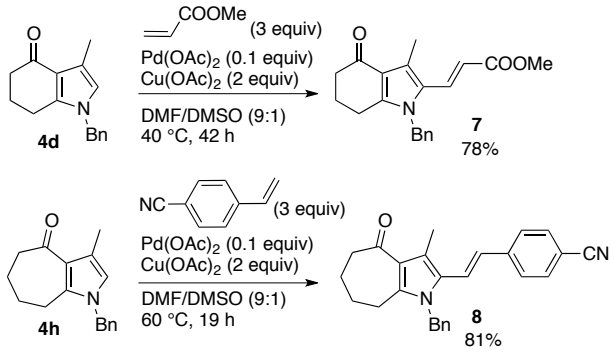
The aza-Michael/carbocyclization cascade reaction system was then combined with oxidation by MnO_2 to synthesize 3-

acylpyrroles **4** in one-pot (Table 2).[12] Using our method, annulated and non-annulated 3-acylpyrroles with various substituents including aryl and alkyl groups at the 1-position of the pyrrole were readily obtained. In the one-pot reactions of cyclohexenone with propargylated amines, products with various *N*-substituents **4a**-**4e** were obtained in 55-84% yield (entries 1-6). Reactions of dimethylsubstituted cyclohexenones and cycloheptenone also afforded the tetrasubstituted pyrroles bearing the six-membered ring and the seven-membered ring systems, respectively, (products **4f**-**4h**) in good yields (70-82%, entries 7-11). Note that **4g**, 3-acylpyrrole bearing a quaternary carbon center at the 2-position, which cannot be synthesized or is very difficult to synthesize by previously reported methods,[2,3] however was easily obtained using our method (entries 9 and 10). Reactions of acyclic enones bearing alkyl, aryl, heteroaryl, and ester groups also afforded 3-acylpyrroles **4i**-**4n** with various substitutions at the 2-position and the 3-position in 20-85% yield (entries 12-17), including pyrrole with variation of the acyl group at 3-position of pyrrole (i.e., **4l**, entry 15). Pentasubstituted pyrrole **4o** was also obtained in 50% yield (entry 18). In the reaction of an arylated alkyne, product **4p** was not obtained under the conditions tested (rt to 60 °C for the first step and rt to 50 °C for the oxidation step) probably due to sterical reasons including the potential allylic strain in the transition state to form the corresponding dihydropyrrole. Note that the one-pot synthesis of 3-acylpyrrole reactions were easily performed on gram-scale; 3-acylpyrroles **4a, 4f** and **4g** were obtained in 61% to 81% yields (entries 2, 8, and 10) with the use of a lower loading of propargylated amine **2** and MnO_2.[13]



Scheme 1. Synthesis of 2,5-Dihydrofuran and 3-Acylfuran.

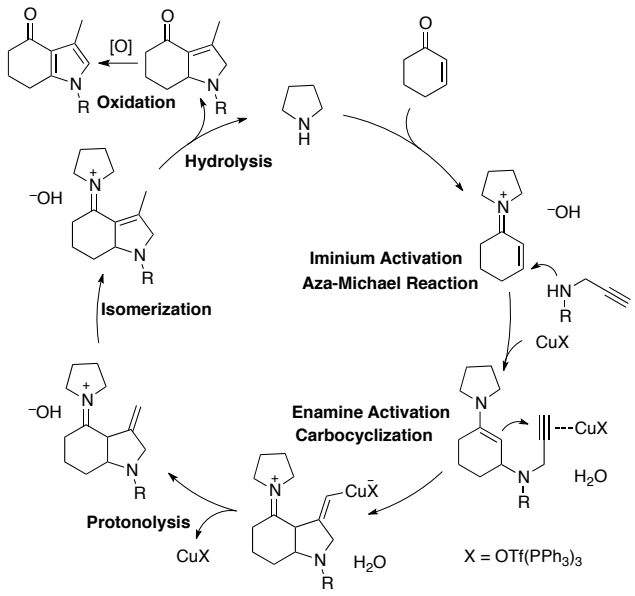
The method was further expanded to the reaction of propargyl alcohol with enone, which gave dihydrofuran **5** in 84% yield, and 3-acylfuran **6** was obtained after oxidation of **5** by DDQ (Scheme 1).



Scheme 2. Transformation to the Fully Substituted 3-Acylpyrroles.

As described above, *N*-substituted 3-acylpyrroles are molecules of interest because of their biological activities and of their uses for the further syntheses of pyrrole-containing derivatives. Thus the tetrasubstituted pyrroles bearing an acyl group at the 3-position were transformed further. For example, pentasubstituted pyrroles were obtained by the introduction of substituents at the 5-position; Pd-catalyzed C-H functionalization of **4d** and **4h** afforded **7** and **8**, respectively (Scheme 2).[14]

A plausible catalytic cycle for the formation of **3** is shown in Scheme 3. The enone is activated by pyrrolidine to generate an iminium ion intermediate for the aza-Michael reaction of substituted propargylamine. The resulting enamine intermediate reacts with the triple bond upon activation by the cupper salt to undergo an intramolecular carbocyclization. Further protonolysis, isomerization, hydrolysis and oxidation give the desired 3-acylpyrrole.



Scheme 3. Plausible catalytic cycle

Conclusions

We have developed efficient methods for the one-pot syntheses of polysubstituted 3-acylpyrroles by cascade reactions from readily available unsaturated ketones and *N*-substituted propargylated amines using cooperative catalyst systems. Substrates with a broad range of functional groups reacted readily, and the method allowed concise, atom-economical assembly of the 3-acylpyrrole frameworks and the 3-acylfuran variant. In addition, the reactions were able to be scaled up to provide the products in good yields in gram-scale for further biomedical research. Use of the reaction systems was also demonstrated by the transformation of the products to the fully substituted 3-acylpyrroles. Further studies on synthetic applications of these methods are ongoing in our laboratory.

Acknowledgements

We thank Dr. Michael Chandro Roy, Research Support Division, Okinawa Institute of Science and Technology Graduate University for mass analyses. This study was supported by the Okinawa Institute of Science and Technology Graduate University and by the MEXT (Japan) Grant-in-Aid for Scientific

Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts".

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and spectral data. See DOI: 10.1039/b000000x/

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