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Synthesis of 4-aryl-2,3-dihydropyrroles via Rh-catalyzed intramolecular hydroamino-methylation reaction

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ABSTRACT

The rhodium-catalyzed intramolecular hydroaminomethylation reaction, generating 4-aryl-2,3-dihydropyrroles, has been developed. Triphenylphosphine has been proved to be the excellent ligand to prepare the dihydropyrrole derivatives in up to 99% yield. This procedure provides an efficient and simple alternative route to synthesize 4-aryl-2,3-dihydropyrrole derivatives only in one step.

N-Heterocyclic moieties are universal skeletons in biologically and physiologically active alkaloids[1] (Fig. 1). 4-Aryl-2,3-dihydrropyrrole derivatives are the key intermediates in the synthesis of (±)-Mesembrine,[2] Elwesine,[3] and other bioactive alkaloids (Fig. 2). Numerous organic methodologies have been developed, in the past decades, but none of them could establish 4-aryl-2,3-dihydrropyrroles only in one step.[4] Long reaction procedures with low to modest yields limited the application of these valuable building blocks in total synthesis.

Hydroaminomethylation is a one-pot tandem reaction, which is a superior methodology over conventional ones from economical and environmental aspects.[5] It firstly generates aldehydes by hydroformylation of alkenes, and then the aldehydes immediately react with primary or secondary amines to provide intermediate imines. The final step is hydrogenation of imine intermediates to obtain the secondary or tertiary amines. Intramolecular hydroaminomethylation of substituted cinnamylamine is a remarkable method to access dihydropyrrole derivatives only in one step. Therefore, in this Letter, we report the rhodium-catalyzed intramolecular hydroaminomethylation with excellent yields (up to 99%).

The hydroaminomethylation of (E)-*N*-benzylcinnamylamine **1a** was initially investigated as a model reaction catalyzed by rhodium complexes bearing representative bidentate or monodentate phosphorous ligands. When **1a** was catalyzed by Xantphos at 80 °C, the expected product **2a** was only yielded 1% (Table 1, entry 1).

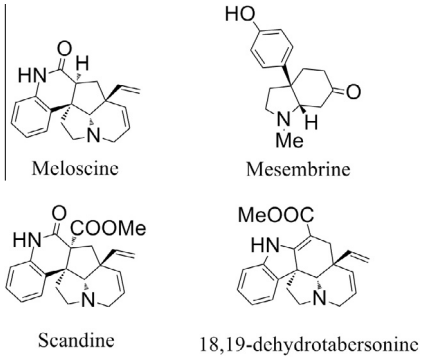

Figure 1. Structures of biologically active alkaloids with pyrrolidine moieties.

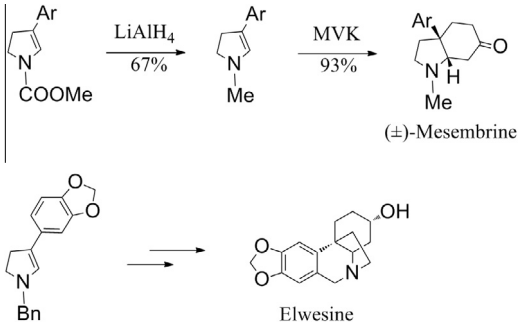

Figure 2. Transformation of 3-aryl dihydropyrrole into bioactive alkaloids.

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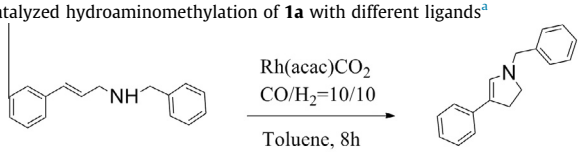
0040-4039/

Table 1
Rh-catalyzed hydroaminomethylation of **1a** with different ligands[a]

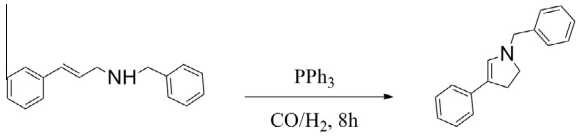


1a **1b**

Entry	Ligand	L/Rh	Yield[b] (%)
1	Xantphos	10	1
2	Bisbi	10	57
3	dppb	10	3
4	$P(OPh)_3$	10	NR
5	$P(o\text{-toyl})_3$	10	11
6	PPh_3	10	83
7	PPh_3	5	78
8	PPh_3	15	67

[a] Reaction conditions: **1a** (1 mmol), $Rh(acac)CO_2$ (0.2 mol %), ligand (2 mol %), total 0.5 mL in toluene at 80 °C for 8 h.
[b] Isolated yield.

Table 2
Optimization of reaction conditions[a]



1a **1b**

Entry	Solvent	Temp (°C)	[Rh]	H_2/CO (bar)	Yield (%)
1	Toluene	80	0.002	20 (1/1)	83
2	EtOAc	80	0.002	20 (1/1)	71
3	Acetone	80	0.002	20 (1/1)	60
4	THF	80	0.002	20 (1/1)	60
5	DCM	80	0.002	20 (1/1)	5
6	Toluene	80	0.002	10 (1/1)	76
7	Toluene	80	0.002	30 (1/1)	81
8	Toluene	80	0.002	20 (1/2)	82
9	Toluene	80	0.002	20 (2/1)	68
10	Toluene	60	0.002	20 (1/1)	40
11	Toluene	80	0.002	20 (1/1)	83
12	Toluene	80	0.002	20 (1/1)	83
13[b]	Toluene	80	0.001	20 (1/1)	99
14[c]	Toluene	80	0.004	20 (1/1)	68

[a] Reaction conditions: **1a** (1 mmol), PPh_3 (2 mol %), total 0.5 mL for 8 h.
[b] PPh_3 1 mol %.
[c] PPh_3 4 mol %.

Other two bidentate ligands Bisbi and dppb also displayed poor reactivates (Table 1, entries 2 and 3). In order to improve the yield, several monodentate phosphorous ligands were chosen for this reaction. No desired product was detected when the reaction was carried out with $P(OPh)_3$ ligand. A remarkable improvement of the yield to 83% was observed by employing PPh_3 as ligand (Table 1, entry 6). Further changing PPh_3/$Rh(acac)CO_2$ ratio (L/Rh) to either 15 or 5 cannot improve the reaction yield (Table 1, entries 7 and 8).

Solvent, as a crucial factor for hydroaminomethylation, was next screened. The results are summarized in Table 2. Toluene was finally chosen as the best solvent (Table 2, entry 1). On the basis of these results, different H_2/CO pressure ratios were tested. When the total pressure increased to 30 bar, the yield was slightly decreased to 81% (Table 2, entry 7). A similar result was obtained when the total pressure decreased to 10 bar. Under 20 bar total syngas pressure constantly, H_2/CO ratio was varied to 1/2 and the yield was comparable with H_2/CO ratio 1/1 (Table 2, entry 8). Increasing H_2 partial pressure cannot further hydrogenate dihydropyrrole to pyrrole, but dramatically dropped the yield to 68% (Table 2, entry 9). Herein, the ratio was 1/1 in 20 bar was the best syngas pressure for this reaction.

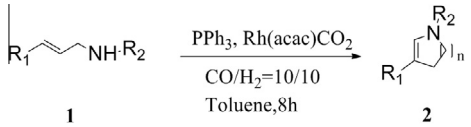
Lowering temperature from 80 °C to 60 °C furnished **2a** in 40% yield (Table 2, entry 10). Surprisingly, decreasing Rh concentration from 0.2 mol % to 0.1 mol % considerably increased the yield to 99% (Table 2, entry 13). However, doubling the metal concentration led to a drop of yield dramatically (Table 2, entry 14). Therefore, the optimal reaction condition was carried out by rhodium complex bearing PPh_3 ligand (1 mol %) in toluene at 80 °C under H_2/CO = 10/10 bar.

With the optimized reaction conditions in hand, a series of **1a** derivatives was successfully converted to desired 4-aryl-2,3-dihydropyrroles with moderate to excellent yields (Table 3). Most of electron-withdrawing substituents at the phenyl ring of the cinnamyl group could generate the final products with excellent yields. The reaction also performed well when varying the amine substituents with different alkyl groups (Table 3, entries 10–12). Notably, the tetrahydropyridine skeleton could be synthesized in excellent yield (90%) (Table 3, entry 15).

Conclusions

In summary, intramolecular hydroaminomethylation provides an efficient alternative approach for the synthesis of 4-aryl-2,

Table 3
Expanding the scope of substrates[a]



1 **2**

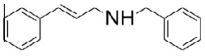
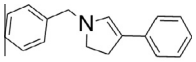
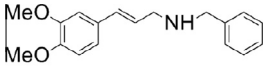
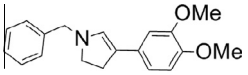
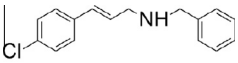
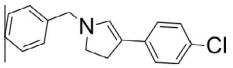
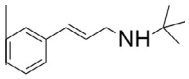
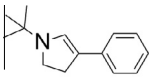
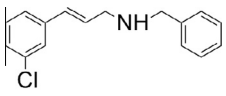
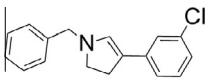
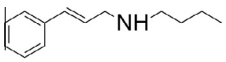
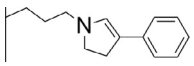
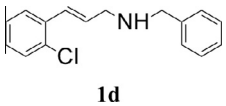
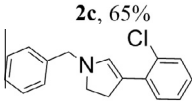
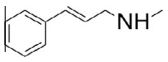
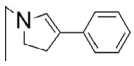
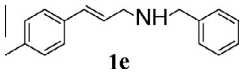
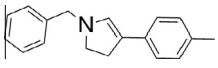
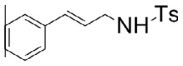
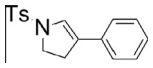
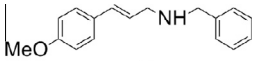
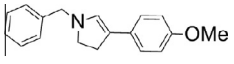
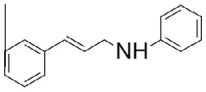
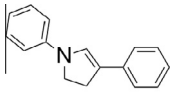
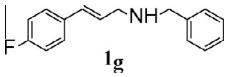
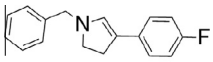
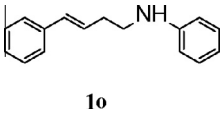
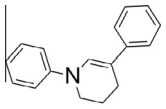
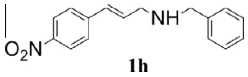
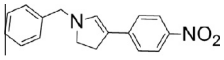
Entry	Substrate	Product	Entry	Substrate	Product
1	 **1a**	 **2a**, 99%	9	 **1i**	 **2i**, 52%
2	 **1b**	 **2b**, 84%	10	 **1j**	 **2j**, 83%

Table 3 (*continued*)

Entry	Substrate	Product	Entry	Substrate	Product
3	 **1c**	 **2c**, 65%	11	 **1k**	 **2k**, 92%
4	 **1d**	 **2d**, 95%	12	 **1l**	 **2l**, 88%
5	 **1e**	 **2e**, 64%	13	 **1m**	 **2m**, 86%
6	 **1f**	 **2f**, 62%	14	 **1n**	 **2n**, 68%
7	 **1g**	 **2g**, 55%	15	 **1o**	 **2o**, 90%
8	 **1h**	 **2h**, 85%			

[a] Reaction conditions: **1** (1 mmol), $Rh(acac)CO_2$ (0.1 mol %), PPh_3 (1 mol %), CO/H_2=10/10, total 0.5 mL in toluene at 80 °C for 8 h.

3-dihydropyrroles only in one step with mild reaction conditions and up to 99% yield.

Acknowledgements

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