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Platinum/Scandium-Cocatalyzed Cascade Cyclization and Ring-Opening Reaction of Tertiary Amines with Substituted Salicylaldehydes to Synthesize 3-(Aminoalkyl)coumarins

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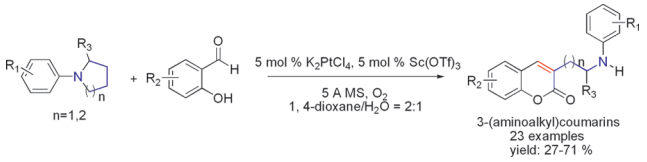

The synthesis of 3-(aminoalkyl)coumarins starting with a platinum/scandium-cocatalyzed oxidative dehydrogenation of α,β-C(sp^3)−H bonds of tertiary amines in the presence of ambient oxygen followed by reactions with substituted salicylaldehydes is revealed. The in situ formed enamines reacted with various salicylaldehydes, which resulted in the development of a one-pot synthetic protocol involving aldol reaction, cyclization, and then ring-opening.

The development of novel methods for the annulation of coumarins is very important in the field of synthetic organic chemistry because coumarins are privileged structures in biological chemistry as well as important structural units found in natural and artificial products.[1] For example, warfarin (**1**) and acenocoumarol (**2**) which are clinically used as anticoagulants and rodenticides, have attracted the interest of synthetic chemists (Figure 1).[1a] Thus far, a variety of useful and efficient synthetic methods have been explored for their synthesis. The major synthetic methods for the preparation of coumarins include the Pechmann reaction,[2] the Knoevenagel condensation,[3] the Wittig reaction,[4] the Claisen rearrangement,[5] the Vilsmeier−Haack and Suzuki cross-coupling reactions,[6] the Pd-catalyzed site-selective cross-coupling reaction,[7] the ring-closing metathesis,[8] and so on. However, these conventional methods are frequently restricted to relatively harsh conditions and cannot be used for substrates with sensitive groups. Thus, an effective method for the straightforward synthesis of 3-(aminoalkyl)coumarins from simple, easily available, and cheap starting materials is still in high demand in modern organic synthesis.

Our group is persistently interested in the oxidation of tertiary amines to prepare various functionalized heterocyclic compounds.[9] We recently reported a mild platinum-catalyzed oxidative dehydrogenation of α and β-C(sp^3)−H bonds adjacent to the nitrogen of tertiary amines to synthesize trisubstituted enamines and chromano[2,3-*b*]piperidines, highlighting the power of Pt catalysis in the oxidation of tertiary amines (Scheme 1a).[9b] Herein, we report a platinum/scandium-cocatalyzed oxidative dehydrogenation of α, β-C(sp^3)−H bonds of tertiary amines with substituted salicylaldehydes giving 3-(aminoalkyl)coumarins, which are reported to have anthelmintic, hypnotic, and insecticidal properties.[10] Tertiary amines are dehydrogenated to give enamines, which react in situ with various salicylaldehydes, resulting in the development of a one-pot synthetic protocol involving aldol reaction, cyclization, and ring-opening (Scheme 1b).

Our study began with the reaction of 1.0 equiv of *N*-phenylpiperidine **1a**, 1.5 equiv of salicylaldehyde **2a**, 0.1 equiv of $PtCl_2$ as catalyst, and 1,4-dioxane/H_2O (2:1) as solvent at 80 °C. To our delight, the desired 3-(aminoalkyl)coumarin **3a** was isolated in 22% yield as a solid. In an attempt to optimize the reaction conditions, other commonly used platinum catalysts were tested in this reaction. Among the platinum catalysts, K_2PtCl_4 gave the best result (Table 1, entry 3). To optimize the yield of the product further, we studied the influence of different reaction media (Table 1, entries 4−6).

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From the results obtained, 1,4-dioxane/H_2O was chosen to be the best solvent (Table 1, entry 3). Then, we screened a variety of additives[9,11] (Table 1, entries 7−10). Among all the additives, $Sc(OTf)_3$ gave the best result. A controlled experiment employing 10 mol % $Sc(OTf)_3$ as the sole catalyst did not lead to product (Table 1, entry 12). After this, we screened the amount of catalyst and additive. When using 5 mol % of K_2PtCl_4 as the catalyst and 5 mol % of $Sc(OTf)_3$ as the cocatalyst, a 71% yield was obtained (Table 1, entry 13). With a series of detailed investigations mentioned above, the optimized reaction conditions were found to be the following (entry 13): 5 mol % K_2PtCl_4 as catalyst, 5 mol % $Sc(OTf)_3$ as cocatalyst, 1,4-dioxane/H_2O (2:1) as mixed solvent, 5 Å molecular sieves as additive, at 80 °C under oxygen atmosphere.

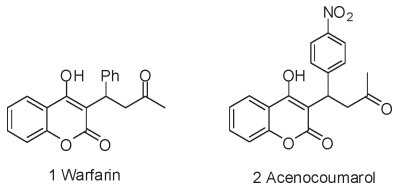
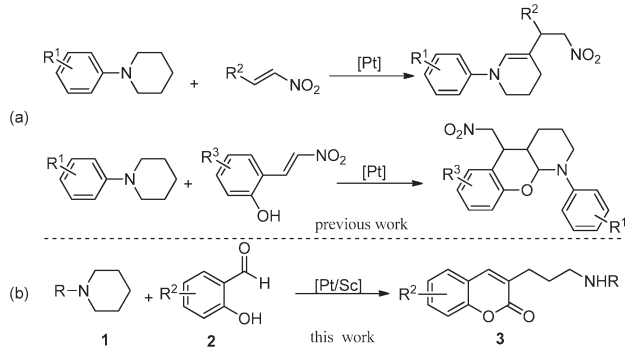


FIGURE 1. Biologically active 3-alkyl coumarins.

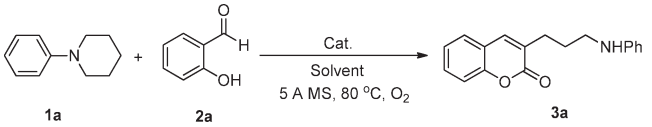
SCHEME 1. Design of a Domino Process



After having established optimized conditions, we extended the scope of this transformation to a wide range of electronically and structurally diverse tertiary amines and substituted salicylaldehydes. The results of these studies are listed in Table 2. Various substituted *N*-phenylpiperidines reacted efficiently with salicylaldehyde, affording **3a**−**k** in 40−71% yields (Table 2, entries 1−11). The protocol is tolerant of both electron-withdrawing and electron-donating substituents in the phenyl moiety of **1**. Sterically demanding ortho substituents can also participate in this reaction, albeit giving lower yields (Table 2, entries 4 and 5). To confirm the structural assignment of products, the relative configuration of the product **3h** was unambiguously assigned by single-crystal X-ray crystallography (see the Supporting Information).[12]

Salicylaldehydes **2*l*−q** bearing a variety of substituents on the benzene ring reacted smoothly to afford the corresponding coumarins **3*l*−q** in 40−53% yields, indicating that the substituents on the aromatic ring of **2** did not have significant influence on the reaction. Salicylaldehydes possessing several functional groups such as methoxyl, methyl, chloro, and *tert*-butyl were also tolerated in this reaction, and moderate yields of corresponding products were obtained. When 4-methyl-1-phenylpiperidine was subjected to the reaction, the corresponding product **3r** was obtained in 53% yield. Under the optimum conditions, 1-(naphthalen-1-yl)piperidine and 1-(naphthalen-2-yl)piperidine were smoothly converted to 3-(aminoalkyl)coumarins **3s** and **3t** in 66% and 49% yields, respectively (Table 2, entries 19 and 20). The size of the ring of the reactant **1** was also tested. *N*-Phenylpyrrolidine exhibited a low reactivity to form **3u** (27%) (Scheme 2). When enantiomerically pure substrate **1v** was used, the cyclization reaction was observed at the 4,5-position of **1v** and desired product **3v** was isolated in a 37% yield with hydroxyl group tolerated and chirality remaining intact. This observation reveals that complex chiral alkamine can be obtained from simple chiral alkamine by using our method. *N*-Phenyl-L-prolinol bearing a benzyl as the protecting group **1w** underwent this transformation with salicylaldehyde, leading to **3w** in 40% yield (Scheme 2).

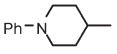
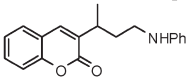
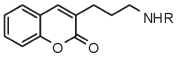
TABLE 1. Optimization of Reaction Conditions[a]



entry	catalyst (mol %)	additive (mol %)	solvent	yield (%)[b]
1	$PtCl_2$ (10)		1,4-dioxane/H_2O = 2:1	22
2	$PtCl_4$ (10)		1,4-dioxane/H_2O = 2:1	12
3	K_2PtCl_4 (10)		1,4-dioxane/H_2O = 2:1	38
4	K_2PtCl_4 (10)		DMF/H_2O = 2:1	26
5	K_2PtCl_4 (10)		THF/H_2O = 2:1	15
6	K_2PtCl_4 (10)		DME/H_2O = 2:1	24
7	K_2PtCl_4 (10)	$Sc(OTf)_3$ (5)	1,4-dioxane/H_2O = 2:1	53
8	K_2PtCl_4 (10)	$Cu(OTf)_2$ (10)	1,4-dioxane/H_2O = 2:1	33
9	K_2PtCl_4 (10)	5 μL of 6 N HCl	1,4-dioxane/H_2O = 2:1	33
10	K_2PtCl_4 (10)	PhCOOH (20)	1,4-dioxane/H_2O = 2:1	45
11	K_2PtCl_4 (10)	$Sc(OTf)_3$ (10)	1,4-dioxane/H_2O = 2:1	40
12		$Sc(OTf)_3$ (10)	1,4-dioxane/H_2O = 2:1	0
13	K_2PtCl_4 (5)	$Sc(OTf)_3$ (5)	1,4-dioxane/H_2O = 2:1	71[c]
14	K_2PtCl_4 (5)	$Sc(OTf)_3$ (5)	1,4-dioxane/H_2O = 2:1	38
15	K_2PtCl_4 (5)	$Sc(OTf)_3$ (5)	1,4-dioxane/H_2O = 2:1	46[d]

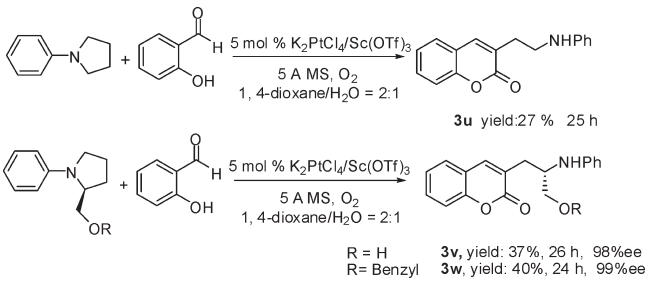
[a]All reactions were carried out by using *N*-phenylpiperidine (0.25 mmol), salicylaldehyde (0.375 mmol), catalyst (0.025 mmol), solvent (2.0 mL), and 5 Å molecular sieves (50 mg) at 80 °C for 20 h; MS = molecular sieves. [b]Yield of isolated product **3a** after column chromatography. [c]**1a**:**2a** = 1:2. [d]**1a**:**2a** = 1:3.

TABLE 2. Scope of the Cascade Cyclization and Ring-Opening Reaction[a]

Entry	R^1	R^2	Product	Time (h)	Yield(%)[b]
1	H	H	**3a**	19	71
2	4-methyl	H	**3b**	25	58
3	3-methyl	H	**3c**	23	39
4	2-methyl	H	**3d**	25	42
5	2-benzyl	H	**3e**	25	40
6	3, 4-dimethyl	H	**3f**	29	58
7	4-methoxyl	H	**3g**	23	50
8	3-methoxyl	H	**3h**	26	50
9	4-chloro	H	**3i**	26	57
10	4-bromo	H	**3j**	25	52
11	3-bromo	H	**3k**	26	50
12	H	5-methyl	**3l**	27	40
13	H	5-methoxyl	**3m**	27	53
14	H	5-tert-butyl	**3n**	24	42
15	H	6-methyl	**3o**	22	48
16	H	3-methyl	**3p**	27	52
17	H	5-chloro	**3q**	28	53
18			**3r**	24	53
19		R=α-naphthalene 	**3s**	27	66
20		R=β- naphthalene	**3t**	29	49

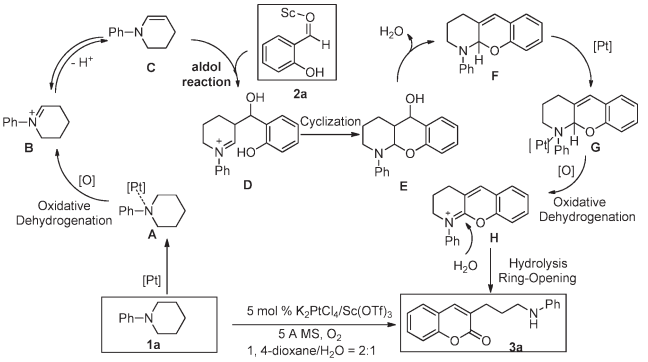
[a]All reactions were carried out by using **1** (0.25 mmol), **2** (0.5 mmol), 5 mol % K_2PtCl_4 (0.0125 mmol), 5 mol % $Sc(OTf)_3$ (0.0125 mmol), 1,4-dioxane/H_2O (2:1, 2.0 mL) and 5 Å molecular sieves (50 mg) at 80 °C under oxygen atmosphere. [b]Isolated yield after column chromatography.

SCHEME 2. Platinum/Scandium-Cocatalyzed Cascade Cyclization and Ring-Opening Reaction of Substituted Tertiary Amines with Salicylaldehyde



A tentative mechanism for the product formation is proposed in Scheme 3. Analogous to pathways for the oxidation of tertiary amines by electrochemical process,[13] metals,[14] and oxidants,[9a,15] the intermediate iminium ion **B** is involved. (1) Platinum coordinates to nitrogen and then goes through activation of the sp^3 C−H adjacent to nitrogen in the presence of oxygen to form an imine-type intermediate **B**. (2) Through β-hydrogen elimination, **B** is converted to α, β-unsaturated compound **C**. (3) The aldol reaction of salicylaldehyde with **C** takes place to give **D**, followed by cyclization leading to intermediate **E**. (4) **E**, when activated by Lewis acids, undergoes dehydration to produce **F**, which is oxidized in the presence of platinum catalyst, oxygen, and water to give **H**. (5) Finally, **H** undergoes hydrolysis and ring-opening to yield the product **3a**.

SCHEME 3. Proposed Mechanism



In summary, we have developed a platinum/scandium-cocatalyzed cascade cyclization and ring-opening reaction of tertiary amines with substituted salicylaldehydes to synthesize 3-(aminoalkyl)coumarins, which are common structural motifs found in many natural products and biologically

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(12) The crystallographic coordinates for **3h** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC-798779. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html. The crystallographic data and CIF of **3h** can be also obtained in the Supporting Information.

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active compounds. On the other hand, this strategy provides a useful approach to synthesize complex chiral alkamine from simple starting material. A plausible mechanism has also been proposed.

Experimental Section

General Procedure for the Preparation of 3-(Aminoalkyl)-coumarins 3a. To a test tube were added *N*-phenylpiperidine (0.25 mmol), K_2PtCl_4 (8.3 mg, 10 mol %), salicylaldehyde (0.50 mmol), and powdered 5 Å molecular sieve (50 mg). The test tube was purged under vacuum and then refilled with oxygen 3 times. 1,4-Dioxane/H_2O = 2/1 (2.0 mL) was then injected, and the mixture was allowed to stir at 80 °C. When the reaction was considered complete as determined by TLC analysis, ethyl acetate (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The residue was purified by flash chromatography on alkalescence silica gel to afford corresponding products **3a** of the indicated compound as a solid: mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.46 (m, 3 H), 7.31 (d, J = 8 Hz, 1 H), 7.23−7.27 (m, 1 H), 7.15−7.19 (m, 2 H), 6.69 (t, J = 7.4 Hz, 1 H), 6.60−6.62 (m, 2 H), 3.78 (s, 1 H), 3.21 (t, J = 6.8 Hz, 2 H), 2.69 (t, J = 7.4 Hz, 2 H), 1.94−2.01 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 153.1, 148.2, 138.9, 130.7, 129.2, 129.1, 127.2, 124.3, 119.4, 117.3, 116.4, 112.7, 43.2, 28.4, 27.9; IR (neat, cm^{-1}) 3408, 3055, 2925, 2854, 1713, 1605, 1505, 1456, 1361, 1266, 1222, 1181, 1086, 1035, 738, 702, 530, 456; HRMS (ESI) m/z calcd for $C_{18}H_{17}NO_2$ (M + H) 280.1332, found 280.1331.

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Supporting Information Available: The detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds and crystallographic data and CIF of **3h** This material is available free of charge via the Internet at http://pubs.acs.org.