ORGANIC LETTERS

2002
Vol. 4, No. 16
2691−2694

Oxidative Cyclization of Amino Alcohols Catalyzed by a Cp*Ir Complex. Synthesis of Indoles, 1,2,3,4-Tetrahydroquinolines, and 2,3,4,5-Tetrahydro-1-benzazepine

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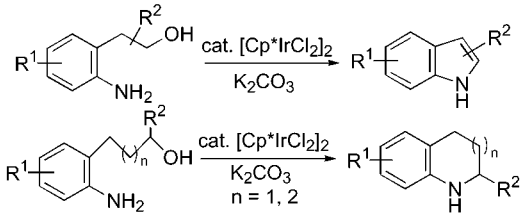
Received May 17, 2002

ABSTRACT



A new iridium-catalyzed oxidative cyclization of amino alcohols has been revealed. Indole derivatives are synthesized in good to excellent yields from 2-aminophenethyl alcohols by means of a $[Cp^*IrCl_2]_2/K_2CO_3$ catalytic system. The present catalytic system is also effective for syntheses of 1,2,3,4-tetrahydroquinolines from 3-(2-aminophenyl)propanols and 2,3,4,5-tetrahydro-1-benzazepine from 4-(2-aminophenyl)butanol.

N-Heterocyclic compounds have attracted considerable attention owing to their functionality in pharmaceutical chemistry, material chemistry, synthetic organic chemistry, and dyes.[1] In particular, the synthesis of benzo-fused *N*-heterocyclic compounds, such as indoles, quinolines, benzazepines, and their saturated derivatives, is very important because their skeletons are found in a variety of natural products, which exert physiological activities. A number of methods for synthesis of indoles have been developed and reviewed.[2] Recently, much attention has focused on the synthesis of indoles by transition-metal-catalyzed *N*-heterocyclization.[3−5] Catalytic systems with palladium,[3d,4a,5b,c,e,g] ruthenium,[3a,b,4b,5a,f] rhodium,[3c,5d] and other metals[2] have been applied for the synthesis of indoles. On the other hand, the catalytic synthesis of 1,2,3,4-tetrahydroquinolines or 2,3,4,5-tetrahydro-1-benzazepines via *N*-heterocyclization has been

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(2) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Pergamon: Oxford, 1996; Vol. 2, pp 119−206. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849. (d) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

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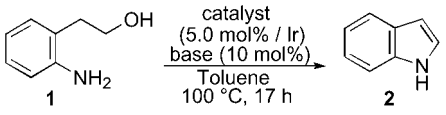
10.1021/ol026200s CCC: $22.00
Published on Web 07/13/2002

hardly explored.[6] During the course of our investigation on the chemistry of pentamethylcyclopentadienyl (Cp*) iridium complexes,[7] we found a catalytic activity of $[Cp^*IrCl_2]_2$ toward hydrogen-transfer reactions between organic molecules and reported Oppenauer-type oxidation of primary and secondary alcohols giving rise to the corresponding carbonyl compounds.[7] In this paper, we wish to report a Cp*Ir complex-catalyzed synthesis of indoles, 1,2,3,4-tetrahydroquinolines, and 2,3,4,5-tetrahydro-1-benzazepine by oxidative *N*-heterocyclization of amino alcohols.

At first, we investigated Cp*Ir-catalyzed oxidative *N*-heterocyclization of 2-aminophenethyl alcohol (**1**) under various conditions. The reactions were performed in the presence of several iridium complexes and bases in toluene as a solvent. The results are summarized in Table 1. Indole

Table 1. Synthesis of Indole (**2**) from 2-Aminophenethyl Alcohol (**1**) by Various Catalytic Systems[a]



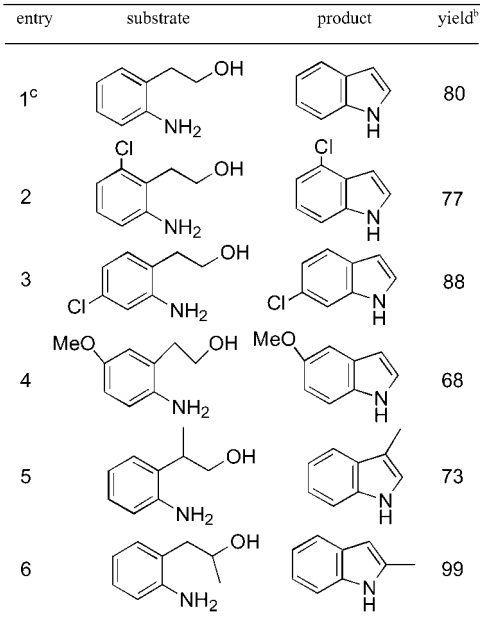
entry	catalyst	base	yield[b] (%)
1	$[Cp^*IrCl_2]_2$	K_2CO_3	70
2[c]	$[Cp^*IrCl_2]_2$	K_2CO_3	90
3	$[Cp^*IrHCl]_2$	K_2CO_3	55
4	$[Cp^*Ir(MeCN)_3][OTf]_2$	K_2CO_3	20
5	$[IrCl(COD)]_2$	K_2CO_3	22
6	none	K_2CO_3	2
7	$[Cp^*IrCl_2]_2$	none	31
8	$[Cp^*IrCl_2]_2$	Li_2CO_3	42
9	$[Cp^*IrCl_2]_2$	^{t}BuOK	62
10	$[Cp^*IrCl_2]_2$	Et_3N	57
11[d]	$[Cp^*IrCl_2]_2$	K_2CO_3	50
12[e]	$[Cp^*IrCl_2]_2$	K_2CO_3	24

[a] The reaction was carried out at 100 °C for 17 h with **1** (1.0 mmol), catalyst (5.0 mol %/Ir), and base (0.10 mmol) in toluene (2 mL). [b] Determined by GC. [c] The reaction was carried out at reflux temperature (111 °C). [d] The reaction was carried out in dioxane. [e] The reaction was carried out in acetonitrile at reflux temperature (81 °C).

(**2**) was formed in a yield of 70% when the reaction was performed at 100 °C for 17 h with use of $[Cp^*IrCl_2]_2$ (5.0 mol %/Ir) and K_2CO_3 (10 mol %) (entry 1). The yield of **2** increased up to 90% when the reaction was performed at reflux temperature (111 °C) (entry 2). Other iridium complexes, $[Cp^*IrHCl]_2$, $[Cp^*Ir(MeCN)_3]^{2+}$, or $[IrCl(COD)]_2$, showed some catalytic activity (entries 3−5), but the yields of **2** were lower than that in the reaction catalyzed by $[Cp^*IrCl_2]_2$. We next examined the effect of base. When the reaction was performed without any base, the yield of **2** declined to 31% (entry 7). Addition of other alkali metal bases (Li_2CO_3, ^{t}BuOK) or organic base (Et_3N) improved the catalytic activity (entries 8−10), but the optimum result was obtained in the reaction with K_2CO_3. Toluene was the solvent of choice, since the reactions in other solvents (dioxane or acetonitrile) gave lower yields of **2** (entries 11 and 12).

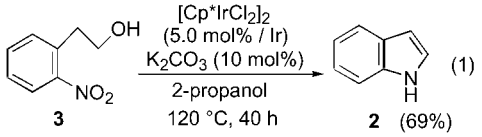
The present oxidative *N*-heterocyclization could be applicable to various amino alcohols, affording indole derivatives. The results are summarized in Table 2.[8] 2-Aminophenethyl alcohols bearing a substituent on the aromatic ring were converted into the corresponding indoles in moderate to high yields (entries 2−4). Indoles bearing a substituent on the *N*-heterocyclic ring could be also synthesized in good to excellent yields by the reaction of 2-aminophenethyl alcohols with a substituent on the methylene chain (entries 5 and 6). In the synthesis of indoles, the reaction proceeded with high selectivity and no indoline product was detected.

Table 2. Synthesis of Indoles from Various Amino Alcohols Catalyzed by the $[Cp^*IrCl_2]_2/K_2CO_3$ System[a]



[a] The reaction was carried out at reflux temperature (111 °C) for 20 h with amino alcohol (1.0 mmol), $[Cp^*IrCl_2]_2$ (5.0 mol %/Ir) and K_2CO_3 (0.10 mmol) in toluene (2 mL). [b] Isolated yield. [c] Reaction time was 17 h.

Since the complex $[Cp^*IrCl_2]_2$ exhibits a catalytic activity toward the reduction of the nitro group to an amino group with use of alcohols as a hydrogen source,[9] we examined the synthesis of indole from 2-nitrophenethyl alcohol (**3**) (eq 1). Indole (**2**) was obtained in the yield of 69% by the

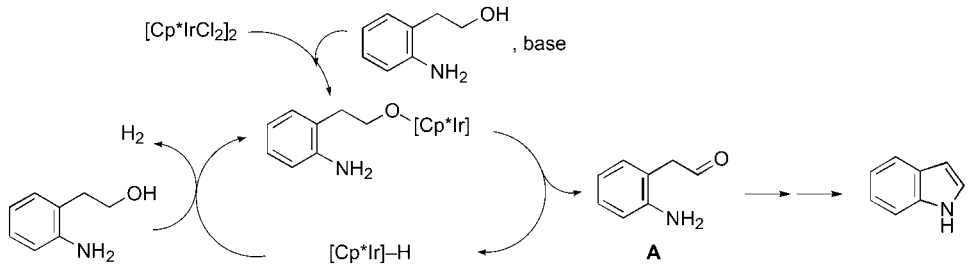


reaction of **3** in 2-propanol at 120 °C for 40 h in a heavy-walled glass reactor. A small amount of 2-aminophenethyl alcohol (**1**) was detected by GC analysis (6%) as a byproduct.

(6) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031 and references therein. (b) Larock R. C.; Berrios-Pena, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509.

(7) Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289.

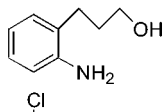
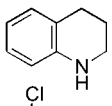
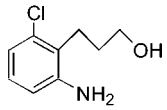
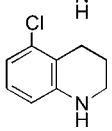
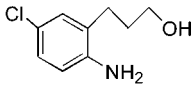
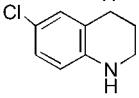
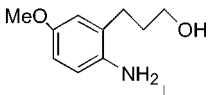
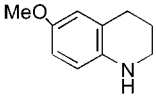
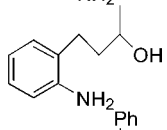
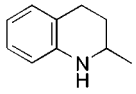
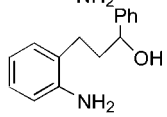
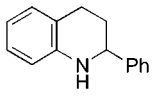
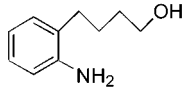
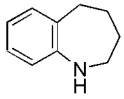
Scheme 1



Thus, it is probable that a catalytic reduction of the nitro group to an amino group occurs initially to give **1**, which is then subjected to *N*-heterocyclization to furnish indole (**2**). Synthesis of indole from **3** is significant because nitro compound **3** as a starting material is more easily available than amino compound **1**. It should be also noted that the Cp*Ir complex acts as a dual catalyst for both the reduction of nitro to an amino group and the oxidative *N*-heterocyclization.

We next examined the *N*-heterocyclization of 3-(2-aminophenyl)propanols. The results are summarized in Table 3.[10] When the present catalytic system was applied to 3-(2-aminophenyl)propanol, 1,2,3,4-tetrahydroquinoline was obtained selectively in almost quantitative yield without any detection of quinoline or dihydroquinolines (entry 1). In this case, the reaction proceeded readily with smaller amounts of catalyst (2.0 mol %/Ir). 3-(2-Aminophenyl)propanols bearing a substituent at the aromatic ring (entries 2−4) or the methylene chain (entries 5 and 6) were converted into the corresponding 1,2,3,4-tetrahydroqunolines in moderate to high yields. In the reactions of entries 5 and 6, small amounts of 2-methylquinoline and 2-phenylquinoline were isolated as byproducts. It should be noted that the present catalytic system was applicable to the synthesis of 2,3,4,5-tetrahydro-1-benzazepine using 4-(2-aminophenyl)butanol as a starting material (entry 7).

Table 3. Synthesis of *N*-Heterocycles from Various Amino Alcohols Catalyzed by the $[Cp^*IrCl_2]_2/K_2CO_3$ System[a]

entry	substrate	product	yield[b]
1[c]			(96)
2[d]			76
3[d]			54
4			64
5			83[e]
6			73[f]
7[g]			71

[a] The reaction was carried out in a heavy-walled glass reactor at 111 °C for 20 h with amino alcohol (1.0 mmol), $[Cp^*IrCl_2]_2$ (5.0 mol %/Ir), and K_2CO_3 (0.10 mmol) in toluene (2 mL). [b] Isolated yield. The values in parentheses are GC yield. [c] 2.0 mol %/Ir of $[Cp^*IrCl_2]_2$ was used. Reaction time was 17 h. [d] Reaction time was 40 h. [e] 9% of 2-methylquinoline was also isolated. [f] 6% of 2-phenylquinoline was also isolated. [g] The reaction was carried out in 0.7 mmol scale.

Although the mechanism for the present reaction is not completely clear as of yet, possible mechanisms are shown in Schemes 1 and 2. That for the catalytic synthesis of indoles is shown in Scheme 1. The first step of the reaction would involve catalytic oxidation of an alcohol to an aldehyde to give an intermediate **A** and a hydrido iridium species. We have already revealed the catalytic activity of $[Cp^*IrCl_2]_2$ toward oxidation of primary and secondary alcohols to the corresponding carbonyl compounds.[7] The intermediate **A** would readily cyclize to afford indoles via intramolecular nucleophilic attack of amino group to carbonyl carbon followed by dehydration, which would be a noncatalytic process. Release of hydrogen in the reaction of the hydrido iridium with 2-aminophenethyl alcohol could regenerate the catalytic active alkoxo iridium species.

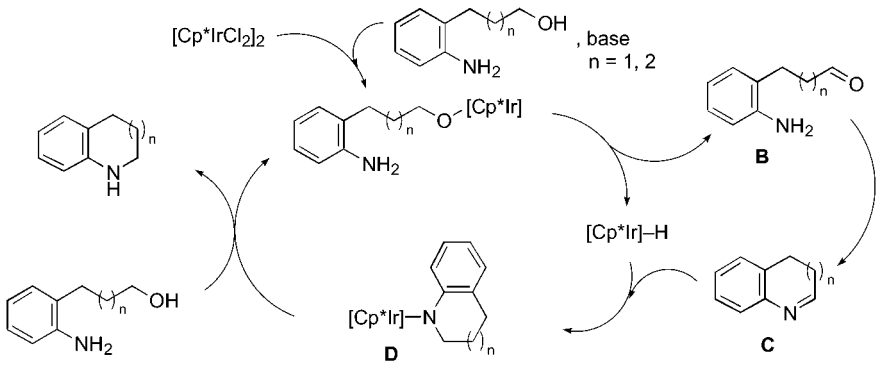
A possible mechanism for the catalytic synthesis of 1,2,3,4-tetrahydroquinolines and 2,3,4,5-tetrahydro-1-benzazepine is shown in Scheme 2. The first step of the reaction affording an intermediate **B** would be similar to that for the synthesis of indoles. The intermediate **B** would transform

(8) Typical procedure: In a glass reactor under an atmosphere of argon, $[Cp^*IrCl_2]_2$ (0.025 mmol) and K_2CO_3 (0.10 mmol) were suspended in toluene (2 mL). Then the substrate (1.0 mmol) was added, and the mixture was stirred under reflux for 20 h. The products were isolated by silica gel column chromatography (eluent: hexane−ethyl acetate). The products were identified by NMR analysis.

(9) Reduction of nitrobenzene (1.0 mmol) in 2-propanol (2 mL) catalyzed by $[Cp^*IrCl_2]_2$ (0.025 mmol) at 120 °C for 17 h gave aniline in 17% yield. Unpublished results.

(10) Typical procedure: In a heavy-walled glass reactor under an atmosphere of argon were suspended $[Cp^*IrCl_2]_2$ (0.025 mmol) and K_2CO_3 (0.10 mmol) in toluene (2 mL). Then the substrate (1.0 mmol) was added and sealed, and the mixture was stirred at 111 °C for 20 h. The products were isolated by silica gel column chromatography (eluent: hexanes−ethyl acetate). The products were identified by NMR analysis.

Scheme 2



into **C** via intramolecular nucleophilic addition and dehydration. Then addition of the hydrido iridium to an iminic C═N bond of **C** would occur to give an amido iridium intermediate **D**. The intermediate **D** would react with an amino alcohol to give a product and regenerate the catalytic active alkoxo iridium species. The base (K_2CO_3) would stimulate the oxidation at the first step as we have already reported.[7]

In summary, we have shown a new catalytic system for the synthesis of indoles, 1,2,3,4-tetrahydroquinolines, and 2,3,4,5-tetrahydro-1-benzazepine, which is, to the best of our knowledge, the first example of the oxidative *N*-heterocyclization of amino alcohols catalyzed by iridium complexes. The present catalytic system would provide a new and useful method for the synthesis of various *N*-heterocyclic compounds.

Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026200S