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Catalytic Hydrogenation of Halosteroidal Derivatives by Bipyridine or Phenanthroline Complexes of Copper(II) in Hydrazine Aqueous Media

Huang-Chi Du, Kung-Cheng Liu, and Wen-Shan Li
Institute of Chemistry, Academia Sinica, Taipei, Taiwan

Abstract: We report two synthetic systems, $Cu(Bpy)^{2+}$ and $Cu(Phen)^{2+}$, for catalytic hydrogenation of steroidal haloalkenes in the presence of hydrazine and air. These studies demonstrated that the selective hydrogenation is faster for the 1,10-phenanthroline–Cu(II) system because forming more stable copper complex are formed, leaving fewer free copper ions in solution. Evidence also supports that the catalytic power of Cu(II) ions can be tuned moderately through the addition of bidentate ligand, Bpy or Phen.

Keywords: Catalytic hydrogenation, dehalogenation, 17β-halosteroids, ligand, steroidal haloalkenes

INTRODUCTION

Several steroidal haloalkanes are well known as antiestrogens for the treatment of human breast tumors and probes for nuclear imaging of estrogen receptors.[1–4] Recently, new types of steroidal estrogen-based antagonists were developed because of the side effects of the partial estrogenic activity of Tamoxifen,[5] the most widely used drug in breast cancer patients for more than 30 years. For example, the compound EM-139[6,7] and ICI 182,780 (Faslodex™),[8–12] bearing either a chlorine at the 16α-position or a pentafluoropentylsulfinyl group at the 7α-position, demonstrate complete

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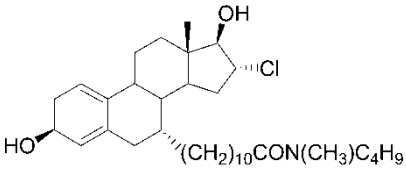
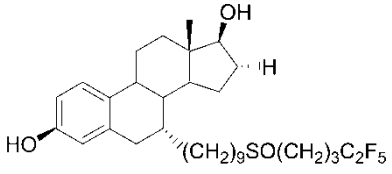
Address correspondence to Wen-Shan Li, Institute of Chemistry, Academia Sinica, Taipei 11529, Taiwan. Tel.: +886-2-27898662; Fax: +886-2-27831237; E-mail: wenshan@chem.sinica.edu.tw

endocrine blockade and activity against Tamoxifen-resistant estrogen receptor-positive tumors. In addition, steroidal haloalkanes substituted with halogens in the D-ring also serve as imaging agents to monitor the hormone responsiveness of the tumor cell and provide early detection and accurate assessment of the disease.[13–18] Similarly, steroids bearing a halogen in the D-ring at C-17β may have the broad range of biological activity to act as new halosteroidal antiestrogens or imaging agents.



EM-139



ICI 182,780

Preparation of 17β-fluoro compounds is easily constructed by replacing the oxygen function (triflate) at C-17β by nBu_4NF; however, synthesis of 17β-chloro, 17β-bromo, and 17β-iodo by halogen substitution at C-17β generates alkenes from elimination instead of substitution of the 17α-triflate. Furthermore, construction of 17β-chloro, 17β-bromo, and 17β-iodo by metal-mediated hydrogenation of vinyl halide is quite complicated because of low yields and production of dehalogenation side products. For instance, palladium-catalyzed hydrogenation of 17-bromo-5α-androstan-16-ene resulted in 5α-androstane (85%) as a major product and 17β-bromo-5α-androstane at low yield (10%).[19] Lately, we demonstrated a mild and selective method to synthesize 17β-halosteroids through Cu(II)/Fe(III)-mediated hydrogenation of steroidal haloakenes in the presence of hydrazine hydrate. This methodology avoids side products from dehalogenation or competing substitution and provides the desired 17β-halosteroids in high yields (90–98%).[20]

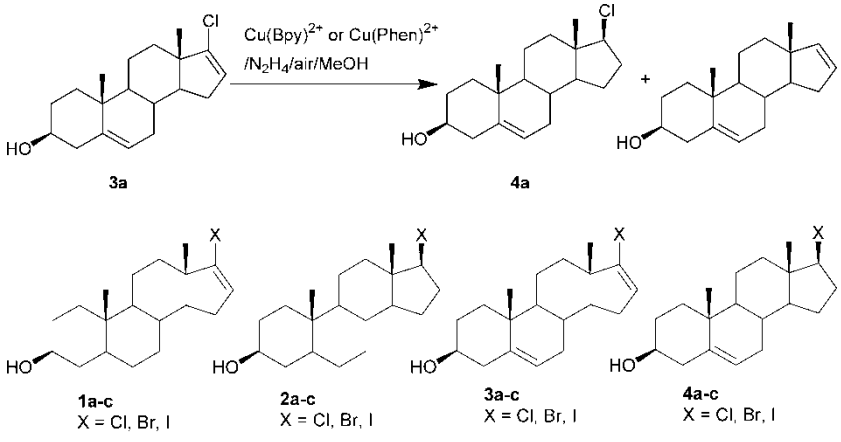
However, the Cu(II)/Fe(III) system has a drawback: it consumes 2 equiv. of Fe(III) during the reaction. For environmental reasons, it is more practical to conduct the system with only a catalytic amount of Cu(II) without the assistance of excess Fe(III). To accomplish this goal, we have to enhance the selectivity of catalytic power of Cu(II) through the aid of coordination chemistry, which already exists in nature. From enzymatic point of view, nature uses the amino nitrogen and the carboxylate oxygen to coordinate the Cu(II) ion at the active site of many metalloenzymes.[21] Because of the hydrophobic and hydrophilic environment of the amino acid network, copper metal in the active site of enzyme can preferentially promote catalytic reactions, such as hydrolysis and coupling reactions, from one course and prevent the undesired contact from the other direction. In the Cu(II)/Fe(III)-mediated hydrogenation system, however, the role of free Cu(II) is still ambiguous, and it is very attractive to explore how free Cu(II) or ligand Cu(II)

complexes manipulate the metal-catalyzed hydrogenation of steroidal haloalkenes. To unravel these questions, we report here a detailed investigation of 2,2′-bipyridine (Bpy)–Cu(II) and 1,10-phenanthroline (Phen)–Cu(II) systems in comparison with the free Cu(II) or Cu(II)/Fe(III) catalytic method described earlier in our laboratory.

RESULTS AND DISCUSSION

Previously, metal-mediated hydrogenation of steroidal haloakenes showed that free $Cu(OAc)_2$ (0.1 equiv) is capable of catalyzing hydrogenation of 17-bromo-3β-hydroxy-5α-androstan-5,16-ene (1.0 equiv) into 17β-bromo-3β-hydroxy-5α-androstan-5-ene (9%) and 3β-hydroxy-5α-androstan-5-ene (43%).[20] However, the desired hydrogenation product is minor, and the dehalogenation one is the major. On the other hand, exclusive $K_3Fe(CN)_6$ (1.5 equiv) as a metal catalyst is very inert at the same condition. Despite of problems of using the metal catalyst individually, metal complex Cu(II)/Fe(III) (0.01 equiv:2.0 equiv) has higher catalytic activity for production of 17β-halosteroids without any concomitant formation of dehalogenation products.[20] Obviously, $K_3Fe(CN)_6$ is able to adjust the catalytic power of Cu(II) and regulate the ratio of final products (hydrogenation/dehalogenation). It is very interesting to see whether the addition of Bpy or Phen ligand[22–24] in Cu(II) is capable of doing the same function in this catalytic system (Scheme 1). The structures of steroidal haloakenes and the corresponding products described in this study are presented in Scheme 1.

We first examined the efficacy of 10 mol% of $Cu(Bpy)^{2+}$ or $Cu(Phen)^{2+}$ as a catalyst to carry out the hydrogenation of 17-chloroalkenes (**1a** and **3a**). The bidentate Bpy or Phen ligand (1 equiv) was mixed with 1 equiv of



Scheme 1.

$Cu(OAc)_2$ and in situ generated mononuclear complex $Cu(Bpy)^{2+}$ or $Cu(Phen)^{2+}$, which was examined for its catalytic hydrogenation in the presence of hydrazine hydrate and air in methanol. Thus, 17-chloroalkenes (**1a** and **3a**) were the first interesting targets to investigate because of their higher heterolytic bond dissociation energy of C–Cl bond; that is, the heterolytic bond dissociation energy is greater for the C–Cl bond than for the C–Br/C–I bonds. In comparison to the absence and presence of Bpy or Phen ligand with $Cu(OAc)_2$ (Table 1, entries 1–3), the ratio of products (hydrogenation/dehalogenation) increased from 0.7 (without ligand) to 7.3 (with Phen ligand), indicating that enhancement of catalytic hydrogenation occurs in the presence of Bpy or Phen. In other words, the abilities of catalytic hydrogenation displayed by $Cu(Bpy)^{2+}$ and $Cu(Phen)^{2+}$ for **1a** were increased three- to ten-fold when compared with $Cu(OAc)_2$ itself. Similarly, the relative yields of **4a** listed in Table 1 (entries 4–6) were found to increase from 66% to 97% with an addition of ligand in the following order: no ligand < Bpy < Phen. The $Cu(Bpy)^{2+}$ or $Cu(Phen)^{2+}$ complex exhibited enhancements in the abilities of catalytic hydrogenation by factors of four to 17-fold relative to those of $Cu(OAc)_2$. The increasing propensity of the catalytic hydrogenation based on the ratio of products is in accordance with the tendency of stability constants of $Cu(Bpy)^{2+}$ and $Cu(Phen)^{2+}$ complexes, where their overall

Table 1. Catatlytic hydrogenation of **1a** and **3a** by $Cu(OAc)_2$ in the presence or absence of ligands[a]

Entry	Ligand	Substrate	Product	Yield (%)[b]	Ratio[c]
1	—	**1a**	**2a**	42	
			dehalogenation	58	0.7
2	Bpy	**1a**	**2a**	67	
			dehalogenation	33	2.0
3	Phen	**1a**	**2a**	88	
			dehalogenation	12	7.3
4	—	**3a**	**4a**	66	
			dehalogenation	34	1.9
5	Bpy	**3a**	**4a**	87	
			dehalogenation	13	6.7
6	Phen	**3a**	**4a**	97	
			dehalogenation	3	32

[a]Reactions were performed at room temperature in methanol (3 mL) for 27 h with substrate **1a** or **3a** (70 mmol), $Cu(OAc)_2$ (7 mmol), and ligands (7 mmol) in the presence of hydrazine hydrate and air.

[b]Determined from the integral ratio of ^1H NMR.

[c]The value of ratio is the yield of hydrogenation product/yield of dehalogenation product.

formation constants are about 10^{17} and 10^{20} in solution respectively.[25] This evidence suggests that more free Cu(II) in solution results in less hydrogenation product and additional formation of dehalogenation. Meanwhile, $Cu(Bpy)^{2+}$ and $Cu(Phen)^{2+}$ complexes entice induction of thermodynamic stability and promote desired orientation for a selective catalytic pathway by a coordination chemistry approach.

In the case of 17-iodoalkenes (**1c** and **3c**), under typical hydrogenation conditions, dehalogenation products (Table 2, entries 1, 4, 12) are usually generated because of the low dissociation energy of C–I bond. Thus, it is necessary to explore various reaction conditions for hydrogenation of **1c**/**3c** using Cu(II)–ligand complex in the presence of $K_3Fe(CN)_6$ to scrutinize the influence of Bpy or Phen on selective hydrogenation. Obviously, with the addition of different amounts of $K_3Fe(CN)_6$ in solution the desired hydrogenation product **2c** had been consistently increased with less formation of dehalogenation product. After optimization, we were able to build up a suitable and practical condition (entry 8) for the catalytic hydrogenation of **1c** (entries 2, 3, 5–7, 8–10). The reaction with $Cu(OAc)_2/Bpy/K_3Fe(CN)_6$ (the molar ratio is 0.1:0.1:0.4) yielded 17β-iodoalkane **2c** in 50% yield with an equal amount of the deiodomination compound (entry 8). Similarly, we then examined the efficacy of $Cu(OAc)_2/Phen/K_3Fe(CN)_6$ as a catalyst for the formation of 17β-iodoalkane **4c** (entries 11–18). We found that the best protocol for the catalytic hydrogenation of **3c** was obtained using the same molar ratio (0.1:0.1:0.4) of $Cu(OAc)_2/Phen/K_3Fe(CN)_6$ in the presence of hydrazine hydrate and air (entry 16). In this event, **4c** was detected in 72% yield, and the other deiodomination product was observed in 12% yield only. Elongation of the reaction time definitely increased the yield of hydrogenation product **4c** up to 87% (entry 19).

Using this protocol, we were able to evaluate the efficacy of Bpy or Phen as a part of the catalyst to catalyze hydrogenation of bromo- and iodo-steroidal compounds (**1b**, **3b**, **1c**, and **3c**). Interestingly, the catalyst with Phen ligand also displayed a higher ratio of hydrogenation products than those of Bpy ligand (Table 3). For example, the ratios of hydrogenation/dehalogenation increased from 2.6 to 3.5 in the cases of entries 1 and 2, from 4.3 to 7.4 in the cases of entries 3 and 4, from 1.0 to 2.0 in the cases of entries 5 and 6, and from 1.1 to 6.0 in the cases of entries 7 and 8. These results are consistent with the observations in Table 1 in the absence of $K_3Fe(CN)_6$ as the catalyst. In addition, evidence demonstrates that the catalytic ability of the Cu(II) ion in hydrogenation of steroidal haloalkenes can be tuned comparatively by adding the Bpy or Phen ligand.

CONCLUSIONS

In conclusion, a practical protocol has been developed that allowed us to evaluate the roles of Bpy and Phen ligands toward Cu(II) metal through the manipulation of thermodynamic stability and reconstruction of the catalytic

Table 2. Selected optimization conditions for 17β-iodosteroids (**2c** and **4c**) formations[a]

Entry	Substrate	Metal oxidant	Ratio (nmol)	Reaction time (h)	Yield (%)[b]	
					2c or **4c**[c]	Dehalogenation
1	**1c**	Cu(II)/Bpy	0.01:0.01	1.0	8	86
2	**1c**	Cu(II)/Bpy/Fe(III)	0.01:0.01:0.02	1.0	12	11
3	**1c**	Cu(II)/Bpy/Fe(III)	0.01: 0.01: 0.1	1.0	9	7
4	**1c**	Cu(II)/Bpy	0.1:0.1	2.0	0	100
5	**1c**	Cu(II)/Bpy/Fe(III)	0.1:0.1:0.02	4.0	14	74
6	**1c**	Cu(II)/Bpy/Fe(III)	0.1:0.1:0.2	4.0	22	40
7	**1c**	Cu(II)/Bpy/Fe(III)	0.1:0.1:0.4	4.0	47	28
8	**1c**	Cu(II)/Bpy/Fe(III)	0.1:0.1:0.4	9.0	50	50
9	**1c**	Cu(II)/Bpy/Fe(III)	0.1:0.15:0.4	4.0	28	39
10	**1c**	Cu(II)/Bpy/Fe(III)	0.1:0.15:1.0	6.0	20	51
11	**3c**	Cu(II)/Phen/Fe(III)	0.01:0.01:0.1	1.0	15	16
12	**3c**	Cu(II)/Phen	0.1:0.1	2.0	2	11
13	**3c**	Cu(II)/Phen/Fe(III)	0.1:0.1:0.2	4.0	55	25
14	**3c**	Cu(II)/Phen/Fe(III)	0.1:0.2:0.2	4.0	53	31
15	**3c**	Cu(II)/Phen/Fe(III)	0.1:0.1:0.4	4.0	47	8
16	**3c**	Cu(II)/Phen/Fe(III)	0.1:0.1:0.4	9.0	72	12
17	**3c**	Cu(II)/Phen/Fe(III)	0.1:0.1:1.0	9.0	29	13
18	**3c**	Cu(II)/Phen/Fe(III)	0.2:0.2:0.4	4.0	29	39
19	**3c**	Cu(II)/Phen/Fe(III)	0.1:0.1:0.4	14.0	87	13

[a]Reactions were performed at room temperature in methanol (3 mL) for different time with substrate **1c** or **3c** (70 mmol), $Cu(OAc)_2$ (7 mmol), ligands (7 mmol), and various amounts of $K_3Fe(CN)_6$ in the presence of hydrazine hydrate and air.

[b]Determined from the integral ratio of ^1H NMR.

[c]**2c** is the product for entries 1–10; **4c** is the product for entries 11–19.

Table 3. Optimized catalytic hydrogenation of **1b, c** and **3b, c** by $Cu(OAc)_2$ in the presence of ligand and $K_3Fe(CN)_6$[a]

				Yield (%)[b]		
Entry	Substrate	Catalyst/ ligand	Reaction time (h)	Hydro-genation	Dehalo-genation	Ratio[c]
1	**1b**	Cu(II)/Bpy/ Fe(III)	18	72 (**2b**)	28	2.6
2	**1b**	Cu(II)/Phen/ Fe(III)	18	78 (**2b**)	22	3.5
3	**3b**	Cu(II)/Bpy/ Fe(III)	18	81 (**4b**)	19	4.3
4	**3b**	Cu(II)/Phen/ Fe(III)	18	74 (**4b**)	10	7.4
5	**1c**	Cu(II)/Bpy/ Fe(III)	9	50 (**2c**)	50	1.0
6	**1c**	Cu(II)/Phen/ Fe(III)	9	62 (**2c**)	31	2.0
7	**3c**	Cu(II)/Bpy/ Fe(III)	9	47 (**4c**)	42	1.1
8	**3c**	Cu(II)/Phen/ Fe(III)	9	72 (**4c**)	12	6.0

[a]Reactions were performed at room temperature in methanol (3 mL) for 9 or 18 h with substrate **1b**, **3b**, **1c**, or **3c** (70 mmol), $Cu(OAc)_2$ (7 mmol), ligands (7 mmol), and $K_3Fe(CN)_6$ (28 mmol) in the presence of hydrazine hydrate and air.

[b]Determined from the integral ratio of ^1H NMR.

[c]The value of ratio is the yield of hydrogenation product/yield of dehalogenation product.

orientation. The catalyst with Phen ligand displays more catalytic power during selective hydrogenation of halosteroidal compounds. Studies to facilitate the selectivity between hydrogenation and dehalogenation by $Cu(OAc)_2$ using more rigid ligands are under way in our laboratory.

EXPERIMENTAL

General

^1H spectra were recorded on a Bruker AMX400 spectrometer. Proton chemical shifts (δ) are reported in parts per million (ppm) relative to the methine singlet at 7.24 ppm for the residual $CHCl_3$ in the deuteriochloroform. The water used in this study was deionized and doubly distilled. All chemicals and solvents were purchased from Sigma, Aldrich, or Acros Organics.

Synthesis of steroidal haloalkenes (**1a**–**c** and **3a**–**c**) was conducted in two steps as described previously.

General Hydrogenation Method

Vinyl halide (70 mmol) was added to a stirred solution of $Cu(OAc)_2$ (1.3 mg, 7.0 mmol) and ligand (7.0 mmol) in methanol (3 mL) under an atmosphere of air at room temperature, then $N_2H_4 \times H_2O$ (200 μL). $N_2H_4 \times H_2O$ (200 μL) was slowly added every 2 h, and the solution was allowed to stir continuously. We stopped the reaction when TLC analysis showed that starting material was gone. The precipitate was filtered and washed thoroughly with dichloromethane. The organic layer was evaporated, and dilute aqueous HCl was added to the remaining aqueous phase adjust the pH to 8–8.5. The resulting water solution was extracted with CH_2Cl_2 (6 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was evaporated, and the small amount of mixture was then directly analyzed by ^1H NMR to determine the ratio of hydrogenation product. The pale yellowish residue was purified by chromatography on silica gel. Elution with hexane first and then a mixture of EtOAc/hexane (1:10 v/v) yielded the corresponding products in order of increasing polarity: the dehalogenation product followed by hydrogenation product as a colorless solid.

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