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A selective Cu(II)/Fe(III)-mediated hydrogenation of steroidal haloalkenes in the presence of hydrazine

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Abstract—A new system for hydrogenation of haloalkenes is reported. Cu(II)/Fe(III)-mediated selective hydrogenation of steroidal haloalkenes in the presence of hydrazine proves to be a very efficient method for the synthesis of 17β-halosteroids, potential candidates as antiestrogens or androgen receptor-mediated imaging agents. The reaction stereospecifically affords β-haloalkanes without any concomitant formation of dehalogenation products.

There are significant therapeutic interests associated with steroidal haloalkanes because of their demonstrated value as antiestrogens for the treatment of breast cancer[1,2] and their binding affinity as imaging agents[3,4] for the androgen receptor. Katzenellenbogen and co-workers have also shown that steroidal haloalkanes, especially at the 16α-position from halogenation of the D ring of the steroid skeleton, display great binding affinities for the lamb and rat uterine estrogen receptors.[5,6] Likewise, steroids bearing a halogen at C-17β in the D ring have the potential to act as imaging agents or new halo-steroidal antiestrogens. However, only the replacement of an oxygen function at C-17β by fluorine has been studied,[4] because fluorine substitution at C-17β is readily accessible by synthesis. The preparation of other C-17 halo compounds, e.g. 17β-chloro, 17β-bromo and 17β-iodo, is quite troublesome. Furthermore, recently we have utilized 17α-bromo-3α-(triphenylsilyloxy)-5α-androstan-6-one to confirm the capability of the steroid skeleton to facilitate relatively long-range through-bond intramolecular energy transfer.[7] Thus, the analogous 17β-halo substrates are the next interesting targets to study. Practically, 17β-fluoro and 17α-halo derivatives are obtained by either hydrogenation of the vinyl fluorides using Pd/C as a catalyst or displacement of the activated 17β-triflate with halogen ion. However, employment of either method to prepare 17β-chloro, 17β-bromo and 17β-iodo suffers from low yields and side reactions; for example, palladium-catalyzed elimination of the halogen moiety[8] and alkene formation from elimination instead of substitution of the 17α-triflate. Several other methods, such as substitution of the 17β-acetoxy group[9] and hypoiodite reaction of 20-hydroxy steroids,[10–12] are reported to give 17β-bromo and 17β-iodo steroids. However, these methods incorporate very tedious chiral separation of diastereomeric intermediates or provide no information on yields. Diimide, produced from hydrazine oxidation, is a well-known *cis*-specific reducing agent. Although significant progress has been made on diimide reduction of olefins to alkanes,[13–24] the reduction of vinyl bromide with diimide is inevitably retarded.[25] Despite numerous attempts to overcome these drawbacks, to the best of our knowledge, no versatile synthesis of 17β-chloro, 17β-bromo and 17β-iodo steroids has yet been reported. This paper discloses a new alternative synthetic protocol to allow the production of highly desired 17β-halo steroids from steroidal haloalkenes.

We have recently explored the selective reduction of the vinyl bromide group in 17-bromo-3β-hydroxy-5α-androstan-5,16-diene (**1b**) to 17β-bromoalkane **2b**, keeping the 5-ene intact, by a combination of copper(II) acetate and hexacyanoferrate(III) complex in the presence of hydrazine and air under mild conditions. The reaction of **1b** with Cu(II)/Fe(III) complex was carried out under various reaction conditions to confirm the optimum conditions (Table 1).

As can be seen by the results summarized in Table 1, the copper complex has higher catalytic activity for the present reaction (entry 1), while Fe(III) complex was inert (entry 2). Upon addition of $Cu(OAc)_2$ in 0.1

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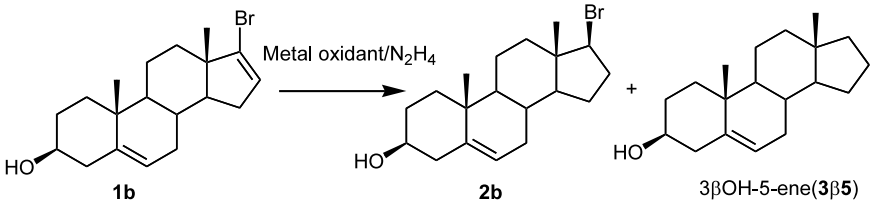
Table 1. Selective hydrogenation of **1b** by Cu(II)/Fe(III) complex[a]



Entry	Metal oxidant	Ratio (mmol)	Reaction time (h)	Yield (%)[c]	
				2b	**3β5**
1	$Cu(OAc)_2$	0.35	24	9	43
2	$K_3Fe(CN)_6$	5.2	24	3	0
3	$Cu(OAc)_2/K_3Fe(CN)_6$	0.035/5.2	24	28	Trace[b]
4	$Cu(OAc)_2/K_3Fe(CN)_6$	0.035/7.0	24	36	0
5	$Cu(OAc)_2/K_3Fe(CN)_6$	0.035/7.0	48	77	0
6	$Cu(OAc)_2/K_3Fe(CN)_6$	0.035/7.0	72	96	0

[a] Compound **1b** (3.5 mmol) was allowed to react with Cu(II)/Fe(III) complex in the presence of hydrazine hydrate and air in methanol (100 mL) at room temperature.
[b] Less than 1%.
[c] Isolated yields.

equiv, the target compound **2b** was obtained only in low yield (9%)(entry 1). In addition, the debromination product 3βOH-5-ene **3β5**, was also formed in 43% yield. A similar result was reported by Cowell et al.[8] when Pd complex was used as a metal catalyst. In the case of the reaction with $Cu(OAc)_2/K_3Fe(CN)_6$ (the molar ratio is 0.035/5.2), 17β-bromoalkane **2b** was obtained in 28% yield with a trace amount of the debromination compound **3β5** (entry 3). Therefore, we decided to decrease the molar ratio of $Cu(OAc)_2/K_3Fe(CN)_6$ to 0.035/7.0. In this event, only **2b** was isolated and no other products were observed (entry 4). Elongation of the reaction time to 48 or 72 h[26] produced 17β-bromoalkane **2b** in 77% or 96% isolated yield. On the basis of these results, the metal oxidant $Cu(OAc)_2/K_3Fe(CN)_6$ at a molar ratio of 0.035/7.0 was deemed to be the most effective complex for use with hydrazine hydrate and air in methanol, and this combination was used in further hydrogenation experiments (Table 2).[27]

Under the hydrogenation protocol, a series of 17-steroidal haloalkenes (Fig. 1, **1a–c**) have been similarly reduced without any formation of dehydrogenation products (Table 2, entry 1). Even with electron-withdrawing halids, high yields (**2a–c**, 94–96%) could be obtained in a reasonable amount of time (24–72 h). This observation is in keeping with the reactivities predicted on the basis of the electronic effect of chloro, bromo, and iodo groups. Similarly, **3a–c**, like **1a–c**, reacted with $Cu(OAc)_2/K_3Fe(CN)_6$ complex under the same conditions to afford **4a–c** in excellent yield (96–97%) with the epoxide moiety intact (entry 2). Obviously, the combination of copper(II) and iron(III) salts are apparently not sufficient Lewis acids to promote the ring opening of the epoxide. 17-Halo-3β-hydroxy-5α-androstan-16-ene (**5a–c**) gave the corresponding 17β-halosteroids, **6a–c**, in 95–98% yield (entry 3). In the case of 17-bromo-3α-(dimethylphenylsiloxy)-5α-androstan-16-ene (**7**), reduction took place exclusively

Table 2. Reaction of various haloalkenes by Cu(II)/Fe(III) complex[a]

Entry	Substrate	Products	X	Time (h)	Yield (%)[b]
1	**1a**	**2a**	Cl	72	94
	1b	**2b**	Br	48	96
	1c	**2c**	I	24	95
2	**3a**	**4a**	Cl	72	96
	3b	**4b**	Br	48	97
	3c	**4c**	I	24	97
3	**5a**	**6a**	Cl	72	95
	5b	**6b**	Br	48	97
	5c	**6c**	I	24	98
4	**7**	**8**	Br	48	90
5	**9**	**10**	H	96	98
6	**11**	**12**	Br	96	80

[a] *Reaction conditions*: Substrate (3.5 mmol) was allowed to react with Cu(II)/Fe(III) complex in the presence of hydrazine hydrate and air in methanol (100 mL) at room temperature.
[b] Isolated yield.

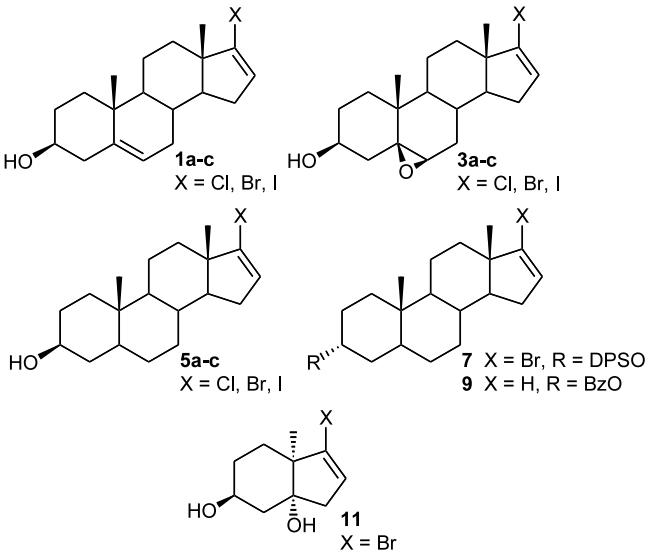


Figure 1. 17-Steroidal haloalkenes and bicyclic bromoalkene used as substrates in the selective hydrogenation.

on the 16-ene in 90% yield, despite the presence of the labile dimethylphenylsiloxy moiety (entry 4). It is noteworthy that 3α-benzoyl-5α-androstan-16-ene (**9**) reacted slowly with $Cu(OAc)_2/K_3Fe(CN)_6$ complex to afford unsaturated 3α-benzoyl-5α-androstane (**10**) in excellent yield (98%) in 96 h (entry 5), although **9** exhibits a lower ionization potential than **5a**–**c**.[22,28] Moreover, the present hydrogenation system was found to be applicable to the synthesis of bicyclic α-bromoalkane (**12**) from $Cu(OAc)_2/K_3Fe(CN)_6$ complex and bicyclic bromoalkene (entry 6). The stereochemistry of C-1 substitution was established by ^1H NMR and molecular mechanics structure modeling. From the knowledge of the known stereochemical specificity of reactions on the D ring of steroids, the incoming diimide[29] in the nucleophilic addition at the C-1 position, prefers to attack the β-side of the five-membered ring, because of the steric bulk of the α-orientated 7-CH_3 moiety.

In summary, we have successfully developed a mild and selective method for the production of 17β-halosteroids. The methodology, which avoids several side reactions such as dehalogenation and competing substitution, is the first example of Cu(II)/Fe(III)-mediated synthesis of 17β-chloro, 17β-bromo and 17β-iodo steroids. These are potential candidates as antiestrogens or androgen receptor-mediated imaging agents. Application of this method to the selective synthesis of acyclic haloalkanes is underway.

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26. The reaction time can totally be shortened to 24 h or less when hydrazine hydrate was frequently added into solution to facilatate the reaction.
27. *General procedure for the synthesis of steroidal haloalkenes (**2a**–**c**, **4a**–**c**, **6a**–**c**, **8**, **10**, **12**)*: To a stirred solution of vinyl bromide (3.50 mmol) and $N_2H_4{\times}H_2O$ (14 mL) in methanol (100 mL) under an atmosphere of air at room temperature was added $K_3Fe(CN)_6$ (2.3 g, 7.00 mmol), then $Cu(OAc)_2$ (7.0 mg, 0.035 mmol). $N_2H_4{\times}H_2O$ (3–5 mL) was added every 12 h until TLC analysis showed that starting material was gone. The precipitate was filtered and washed thoroughly with methanol. The organic layer was evaporated and the remaining aqueous

phase was added dilute aqueous HCl to adjust the pH to 8–8.5. The resulting water solution was extracted with CH_2Cl_2 (3–15 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was evaporated and the pale yellowish solid chromatographed on silica gel in EtOAc/Hexane to afford corresponding compounds. All the new products gave satisfactory spectral data in accord with the assigned stereochemistry.

17β-Iodo-3β-hydroxyandrostan-5-ene (**2c**): Colourless solid; mp 166–167°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (m, 1H), 3.76 (t, 1H, $J=9.3$ Hz), 3.53 (m, 1H), 2.38–2.19 (m, 3H), 2.18–1.97 (m, 2H), 1.90–1.80 (m, 2H), 1.78–1.60 (m, 3H), 1.60–1.40 (m, 3H), 1.37–1.20 (m, 2H), 1.17–0.99 (m, 7H), 0.83 (3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 121.1, 71.6, 50.1, 43.8, 42.1, 41.7, 37.2, 36.6, 34.1, 33.2, 31.7, 31.5, 25.4, 20.7, 19.4, 16.8; LRMS (FAB) m/z: 400 $(M)^+$, 399 $(M-H)^+$, 383 $(M+H-H_2O)^+$, 255 $(M-H_2O-I)^+$; HRMS calcd for $C_{19}H_{29}IO$ $(M)^+$ 400.1263; found, 400.1269.

17β-Bromo-5β,6β-epoxy-3β-hydroxy-5α-androstane (**4b**): Colourless solid; mp 144–145°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, 1H, $J=9.3$ Hz), 3.59 (m, 1H), 3.00 (d, 1H, $J=1.9$ Hz), 2.19 (m, 1H), 2.06–1.82 (m, 4H), 1.78–1.54 (m, 3H), 1.52–1.11 (m, 9H), 0.93 (s, 3H), 0.91–0.77 (m, 2H), 0.73 (s, 3H), 0.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.8, 63.2, 62.9, 61.5, 51.0, 50.5, 43.5, 41.7, 37.0, 36.0, 34.78, 32.2, 32.0, 30.6, 30.5, 24.2, 21.3, 16.9, 13.7; LRMS (FAB) m/z: 371 $(M+H)^+$, 369 $(M+H)^+$, 353 $(M+H-H_2O)^+$, 351 $(M+H-H_2O)^+$; HRMS (FAB) calcd for $C_{19}H_{29}BrO_2$ $(M)^+$ 368.1351; found, 368.1352.

3α-Hydroxy-5β-benzoyl-7α-methyloctahydroindene-1α-bromide (**13**): A benzoyl derivative of product **12**; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 ppm (d, 2H), 7.59 (t, 1H), 7.47 (t, 2H), 5.05–4.99 (m, 1H), 4.42 (t, 1H, $J=6.9$ Hz), 1.50–1.26 (m, 10H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 132.9, 130.3, 129.6, 128.4, 80.1, 71.4, 61.4, 47.6, 39.4, 35.3, 30.6, 29.6, 27.0, 15.8; LRMS (FAB) m/z: 355 $(M+H)^+$, 353 $(M+H)^+$; HRMS calcd for $C_{17}H_{21}O_3Br$ $(M+H)^+$, 353.0752; found, 353.0758.

28. The controversy was also reported by Nelson, D. J., et al. This shows that hydrogen reactions are not exclusively controlled by both electronic and steric effects in the present conditions. Torsional strain and bond angle bending strain may contribute to the observed reactivity differences.
29. It should be noted that hydrogenation of the double bond is not caused by hydrazine itself but by a oxidation product, diimide, of hydrazine.