Iodotrimethylsilane-Mediated 2-Monohalogenation of 4-Aza-5α-androstan-3-one Steroids

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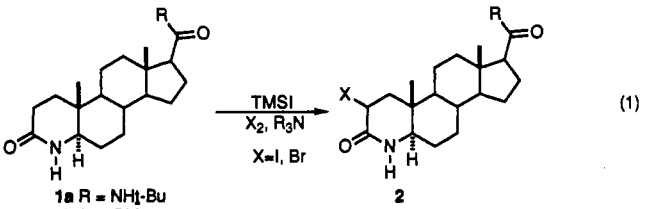
Selective and high-yielding iodotrimethylsilane-mediated 2-monohalogenation of the title compounds is described, and a mechanism for the reaction is proposed. The method provides 2-iodo-4-aza-5α-androstan-3-one steroids in essentially quantitative yields.

Introduction

4-Aza-5α-androstan-1-ene-3-one derivatives are potent inhibitors of 5α-reductase, the enzyme which converts testosterone to dihydrotestosterone. (5α,17β)-*N*-(1,1-dimethylethyl)-3-oxo-4-aza-androstan-1-ene-17-carboxamide is now used for the treatment of prostatic hyperplasia.[1] One of the key functional groups that contributes to the high potency of these compounds is the δ-1 olefin moiety, and methods have been sought for the introduction of this functional group in our laboratories.[2]

As a result of pursuing the above objective, we have uncovered a facile iodotrimethylsilane(TMSI)-mediated 2-monohalogenation of 4-aza-5α-androstan-3-one steroids (eq 1). Although methods for the α-halogenation of



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secondary amides and lactams are known,[3] these procedures did not provide more than a trace of monohalogenated product with our substrates. Except for a recent paper describing the α-iodination reaction of unsaturated amides[3f] where a properly situated double bond in the molecule is required for the chemistry to proceed, we believe that this is the first method for the α-iodination of simple N-monosubstituted amides. We report that the monohalogenation of steroidal substrates **1a-c** and other secondary amides can be carried out under very mild conditions using iodine or bromine in the presence of TMSX and an appropriate amine base. The results of our studies are shown in Table I. Excellent yields were obtained for this conversion under a variety of conditions. As little as 0.5 equiv of TMSI was required to catalyze the complete iodination of **1b** (run 10) which contained no other functional group in the molecule that could consume TMSI. With a second secondary amide function, such as **1a**, it was still possible to obtain the 2-iodo product exclusively by using only 1 equiv of TMSI and 2 equiv of I_2 (run 4). When the amount of TMSI was decreased to 0.2 equiv while maintaining the level of I_2 at 2 equiv, the conversion of **1a** to the 2-iodo product suffered under otherwise similar conditions (run 5). Efficient in situ formation of TMSI by iodine in the reaction mixture is crucial for realization of 100% conversion. For example, even when 5 equiv of TMSBr and 5 equiv of Br_2 were used, the reaction gave a 50/50 mixture of starting material/2-bromo product (run 1). However, by changing the catalyst to TMSI in the bromination, it was possible to push the reaction to completion. The ratio of 2-bromo versus 2-iodo products varied sharply with the amount of Br_2 used. Using 1 equiv of TMSI and 5 equiv of Br_2, the 2-bromo/2-iodo product ratio was 90/10 (run 2) while reducing the amount of Br_2 to 2 equiv gave a 2-bromo/2-iodo ratio of 22/78 (run 3). The halogenation reaction performed equally well in methylene chloride, toluene, or tetrahydrofuran (runs 7, 8, and 9, respectively) with TMEDA as the base. In addition to TMEDA (runs 1-11, 15), Et_3N (run 12) and Et_2NMe (run 13) were also found to be suitable bases for this reaction. Surprisingly, diisopropylethylamine (DIEA) in methylene chloride gave a 59/41 mixture of starting material/2-iodo product (run 14), and only a trace of the 2-iodo product was observed in toluene under similar reaction conditions. We propose that the low solubility of the hydrohalide salts of TMEDA, Et_3N, and Et_2NMe in contrast to DIEA in the above solvents is responsible for these observations. Precipitation of these hydrohalide salts could remove sufficient acid from the reaction to displace the proposed equilibrium shown in Scheme I toward product and allow the reaction to proceed to completion. These reactions must be monitored closely and quenched immediately after completion of halogenation. Overnight aging of the reaction mixtures results in partial to complete regeneration of starting steroids. The mechanism of this reversal is not clear at this time.

It was also possible to utilize TMSI generated *in situ* from TMSCl and I_2 for the iodination reaction. The reaction only proceeded to 80% conversion (run 6) with 1 equiv of TMSCl and 1.5 equiv of I_2, but 100% conversion

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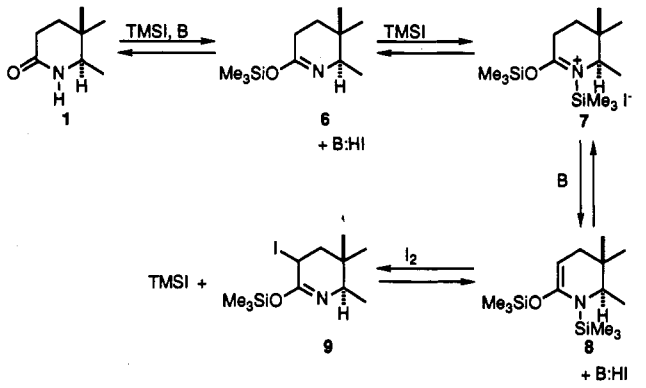
Table I. Iodination and Bromination of 4-Aza-5α-androstan-3-one Derivatives

run[a]	starting amide	molar equiv TMEDA	TMSX	I_2	Br_2	product ratio: starting amide	α-Br	α-I	comment
1	1a	5	Br, 5		5	50	50		
2	1a	5	I, 1		5		90	10	
3	1a	5	I, 1		2		22	78	
4	1a	5	I, 1	2				100	*b*
5	1a	5	I, 0.2	2		25		75	
6	1a	5	Cl, 1	1.5		20		80	
7	1a	3	Cl, 2	1.5				100	*c*
8	1a	3	Cl, 2	1.5				100	*d*
9	1a	4	Cl, 3	2.5				100	*e*
10	1b	5	I, 0.5	2				100	
11	1b	3	Cl, 2	2				100	*f*
12	1a	*g*	Cl, 3	2				100	
13	1a	*h*	Cl, 3	2				100	
14	1a	*i*	Cl, 3	2		59		41	
15	1c	5	Cl, 4	3		2		98	*j*
16	3	3	I, 2	1.5		1		99	*j*
17	4	3	I, 2	1.5				100	*k*
18	5	3	I, 2	1.5				100	*l*

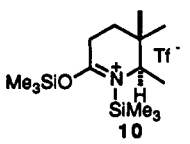
[a] Reactions performed in CH_2Cl_2 at −5 to 0 °C unless noted otherwise. The reaction time varies from 1 to 3 h. The α/β ratio of halogenated products is >95/5. [b] 90% isolated yield. [c] 98% isolated yield. [d] In toluene. [e] In THF at −10 °C. [f] 96% isolated yield. [g] 5 equiv of Et_3N used. [h] 5 equiv of Et_2NMe used. [i] 5 equiv of *i*-Pr_2NEt (DIEA) used. [j] 95% isolated yield. [k] 93% isolated yield. [l] 92% isolated yield.

Scheme I

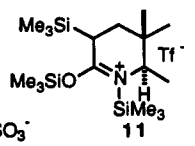


was obtained by increasing TMSCl to 2 equiv while maintaining the I_2 at 1.5 equiv (run 7). Ester and carboxylic acid functional groups at the C-17 position were tolerated in the reaction and afforded the corresponding 2-iodo analogs in excellent yields (run 11 and 15). No dihalogenation was observed in this investigation and no halogenation was observed in the "D" ring. This iodination procedure is quite general and, as shown by runs 16–18, monoiodinated products could be obtained from representative amides such as *N*-benzyl-3-phenylpropionamide (**3**), *N*-phenylpropionamide (**4**), and 2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**5**).[4]

The proposed mechanism for this conversion is outlined in Scheme I. Examination of a mixture of **1b** with TMSI (3 equiv) and TMEDA (3 equiv) in CD_2Cl_2 by ^{13}C NMR showed that the steroid was converted to **6** with no observable evidence for intermediates **7** or **8**. The formation of **10** and **11** was observed, however, when



Tf⁻ = $CF_3SO_3^-$



trimethylsilyl trifluoromethanesulfonate (TMSTf) and DIEA were substituted for TMSI and TMEDA. When TMSTf was added to the steroidal substrate and DIEA, no **8** was observed but rapid trapping of **8** by electrophiles (TMSTf in this case) present in the system could have precluded it from being detected. The spectroscopic study will be presented in a separate article.

We have demonstrated that a TMSI-mediated halogenation reaction can provide various α-iodo and α-bromo lactams and amides in excellent yields. These products can potentially be converted to other functional groups of choice and this method could be of broad utility in the synthesis of halogenated amides and lactams.

Experimental Section

Melting points are uncorrected. All ^1H and ^{13}C NMR spectra were recorded at 300 MHz. The progress of the reactions was followed by high performance liquid chromatography (HPLC) using a Dupont Zorbax C-8 column (25 cm × 4.6 mm) and mixtures of acetonitrile–water containing 0.1% H_3PO_4 as mobile phase. The eluent was monitored at 210 nm.

All chemicals were used as received without further purification. The CH_2Cl_2, toluene, and THF solvents were dried with 4A molecular sieves (water < 50 μg/mL). TMEDA, triethylamine, diethylmethylamine, and DIEA were also dried over 4A molecular sieves.

General Procedure for Iodination with TMSI and TMEDA. A slurry of **1b** (0.67 g, 2 mmol) and TMEDA (1.51 mL, 10 mmol) in CH_2Cl_2 (10 mL) was cooled to −15 °C and TMSI (0.14 mL, 1 mmol) was added. The solution was stirred for 15 min and iodine (1.02 g, 4 mmol) was added as a solid in one portion. The mixture was warmed to 0 °C and kept at this temperature until completion (1.5 h). The reaction mixture was quenched with 10% Na_2SO_3 (10 mL) and saturated aqueous NaCl (10 mL), the organic phase was separated, and the CH_2Cl_2 solvent and volatiles were removed in vacuo at 50 °C. The residue was diluted with CH_3CN (3 mL), and the product was crystallized by the slow addition of water (9 mL). The solid was filtered, washed with water, and dried *in vacuo* at 50 °C. The yield of **2b** (X = I) was 0.88 g (96%): mp 223–224 °C dec; ^1H NMR ($CDCl_3$) δ 6.99 (s, 1H), 4.74 (dd, J = 10.5, 8.0 Hz, 1H), 3.63 (s, 3H), 3.14 (dd, J = 12.4, 3.4 Hz, 1H), 2.56 (dd, J = 13.6, 8.1 Hz, 1H), 2.32 (t, J = 9.1 Hz, 1H), 2.2–1.90 (m, 3H), 1.90–1.57 (m, 4H), 1.57–0.53 (m, 9H), 0.84 (s, 3H), 0.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 169.0, 60.7, 55.0, 54.9, 51.2, 50.6, 48.8, 44.0, 39.2, 37.8, 34.7, 29.2, 26.5, 24.2,

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23.4, 20.8, 18.6, 13.4, 10.9. Anal. Calcd for $C_{20}H_{30}INO_3$: C, 52.29; H, 6.58; I, 27.63; N, 3.05. Found: C, 52.17; H, 6.64; I, 27.41; N, 3.01.

General Procedure for Iodination with TMSCl and TMEDA. A slurry of **1a** (20 g, 5.3×10^{-2} mol) in CH_2Cl_2 (200 mL) and TMEDA (24 mL, 1.6×10^{-1} mol) was cooled to −15 °C with stirring under nitrogen, and TMSCl (13.5 mL, 1.1×10^{-1} mol) was added via a syringe. The slurry was stirred for 5 min and I_2 (20.5 g, 8.1×10^{-2} mol) was added in three portions. The reaction was warmed to −5 to 0 °C and periodically checked for completion (2 h) by HPLC. The reaction was quenched with 10% Na_2SO_3 (100 mL) and 50% saturated NaCl (100 mL). The combined aqueous phases were back-extracted with CH_2Cl_2 (20 mL) and the organic phases combined. Toluene (30 mL) was added to the organic solution. The volume of the solution was reduced *in vacuo* at ≤60 °C to 40 mL and hexane (100 mL) was added slowly at room temperature with stirring. The crystallized solid was filtered, washed, and dried in vacuo at 60 °C to give 26.3 g (98% yield) of **2a** (X = I): mp 230–232 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 1H), 5.09 (s, 1H), 4.71 (dd, J = 10.5, 8.1 Hz, 1H), 3.11 (dd, J = 12.3, 3.2 Hz, 1H), 2.52 (dd, J = 13.6, 8.1 Hz, 1H), 2.20–1.75 (m, 4H), 1.75–1.45 (m, 5H), 1.45–1.10 (m, 5H), 1.28 (s, 9H), 1.10–0.70 (m, 3H), 0.61 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 168.9, 60.6, 57.2, 55.3, 50.8, 50.6, 48.7, 43.5, 39.1, 38.1, 34.5, 29.2, 28.8, 26.5, 24.1, 23.0, 20.9, 18.6, 13.0, 10.9. Anal. Calcd for $C_{23}H_{37}IN_2O_2$: C, 55.20; H, 7.46; I, 25.36; N, 5.59. Found: C, 55.44; H, 7.74; I, 25.15; N, 5.64.

2-Iodo 17-carboxylic acid 2c (X = I): mp 235–238 °C dec; ^{1}H NMR (CD_3CO_2D) δ 4.96 (dd, J = 10.0, 8.3 Hz, 1H), 3.21 (dd, J = 12.4, 3.5 Hz, 1H), 2.62 (dd, J = 13.6, 8.2 Hz, 1H), 2.43 (t, J = 9.6 Hz, 1H), 2.20–1.91 (m, 3H), 1.91–1.64 (m, 4H), 1.64–0.98 (m, 10H), 0.98–0.79 (m, 1H), 0.88 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (CD_3CO_2D) δ 180.1, 173.4, 61.5, 56.1, 55.9, 51.7, 49.4, 45.0, 40.0, 35.8, 30.2, 26.9, 25.0, 24.1, 21.7, 16.5, 14.0, 11.0. Anal. Calcd for $C_{19}H_{28}INO_3$: C, 51.24; H, 6.34; I, 28.50; N, 3.15. Found: C, 51.08; H, 6.28; I, 27.92; N, 3.02.

General Procedure for Bromination with TMSI and TMEDA. A slurry of **1a** (20 g, 53 mmol) in CH_2Cl_2 (200 mL) and TMEDA (40 mL, 265 mmol) was cooled to −15 °C with stirring under nitrogen, and TMSI (6.8 mL, 53 mmol) was added. The slurry was stirred for 15 min and Br_2 (42.4 g, 265 mmol) was added. The reaction was warmed to −5 to 0 °C and periodically checked for completion (3 h) by HPLC. The reaction was quenched with 10% Na_2SO_3 (100 mL) and 50% saturated NaCl (100 mL). The combined aqueous phases were back-extracted with CH_2Cl_2 (20 mL), and the organic layers were combined. Toluene (30 mL) was added to the organic solution and the volume of the solution was reduced *in vacuo* at ≤60 °C to 40 mL and hexane (100 mL) was added slowly at room temperature with stirring. The crystallized solid was filtered, washed, and dried in vacuo at 60 °C to give 22.8 g of a mixture of **2a** (X = Br and I, Br/I = 9/1). An analytical sample of **2a** (X = Br) was obtained by recrystallization from acetonitrile: mp 231–232 °C dec; ^{1}H NMR ($CDCl_3$) δ 6.80 (s, 1H), 5.07 (s, 1H), 4.49 (dd, J = 10.8, 7.7 Hz, 1H), 3.19 (dd, J = 12.2, 3.8 Hz, 1H), 2.55 (dd, J = 13.4, 7.7 Hz, 1H), 2.24–1.80 (m, 4H), 1.80–1.50 (m, 5H), 1.50–1.12 (m, 5H), 1.33 (s, 9H), 1.12–0.78 (m, 3H), 0.88 (s, 3H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 167.8, 60.7, 57.3, 55.4, 51.0, 50.8, 46.5, 43.7, 42.9, 38.7, 38.2, 34.5, 29.2, 28.9, 26.5, 24.2, 23.1, 21.0, 13.1, 11.5. Anal. Calcd for $C_{23}H_{37}BrN_2O_2$: C, 60.92; H, 8.22; Br, 17.62; N, 6.18. Found: C, 60.91; H, 8.16; Br, 17.55; N, 6.20.

***N*-Benzyl-2-iodo-3-phenylpropionamide.** After the usual workup, the product was isolated by crystallization from cyclohexane (0.2 M). The yield was 95%: mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 7.37–7.00 (m, 10H), 6.04 (s, 1H), 4.52–4.28 (m, 3H), 3.56 (dd, J = 14.0, 8.7 Hz, 1H), 3.27 (dd, J = 14.0, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 169.4, 138.6, 137.5, 129.1, 128.6, 127.6, 127.5, 127.1, 44.0, 42.9, 25.5. Anal. Calcd for $C_{16}H_{16}INO$: C, 52.62; H, 4.41; I, 34.75; N, 3.83. Found: C, 52.58; H, 4.30; I, 34.60; N, 3.78.

***N*-Phenyl-2-iodopropionamide.** The product crystallized from cyclohexane (0.2 M) in 93% isolated yield: mp 135–136 °C; ^{1}H NMR (DMSO-d_6) δ 10.22 (s, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.3 Hz, 1H), 4.74 (q, J = 6.8 Hz, 1H), 1.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 169.2, 138.6, 128.7, 123.4, 119.0, 23.1, 19.2. Anal. Calcd for $C_9H_{10}INO$: C, 39.30; H, 3.66; I, 46.13; N, 5.09. Found: C, 39.18; H, 3.46; I, 45.94; N, 5.03.

3-Iodo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. The product crystallized from cyclohexane (0.2 M) in 92% isolated yield: mp 178–179 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 7.38–7.11 (m, 3H), 7.07 (d, 7.8 Hz, 1H), 4.69 (t, J = 9.1 Hz, 1H), 3.10–2.87 (m, 1H), 2.87–2.60 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8, 137.4, 132.7, 129.8, 127.9, 126.3, 122.0, 41.6, 31.6, 23.7. Anal. Calcd for $C_{10}H_{10}INO$: C, 41.84; H, 3.51; I, 44.20; N, 4.88. Found: C, 42.04; H, 3.30; I, 44.04; N, 4.69.

The experimental procedures for using other amines and solvents are similar to the above procedures except that triethylamine, diethylmethylamine, or DIEA is used in place of TMEDA, and CH_2Cl_2 is substituted with toluene or THF.