Reductive Cleavage of Heteroaryl C−Halogen Bonds by Iodotrimethylsilane. Facile and Regioselective Dechlorination of Antibiotic Pyrrolnitrin

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Iodotrimethylsilane (Me_3SiI) is a commercially available reagent and, as an inexpensive in situ alternative, can be easily prepared by treatment of chlorotrimethylsilane (Me_3SiCl) with sodium (or lithium) iodide in acetonitrile (as an Me_3SiI equivalent)[1] or without any solvents[2] under mild conditions. This reagent has been widely used for the cleavage of the C−O bonds in esters (including lactones, carbamates, and phosphonates) and ethers (including epoxides and acetals) leading to the corresponding iodides and carboxylic acids or alcohols as the ultimate products, as well as for the conversion of alcohols into the corresponding iodides and for the deoxygenation of sulfoxides.[3,4] These chemical properties of Me_3SiI are due to the weak Si−I bond and an intrinsic high affinity of the silicon atom for the oxygen atom. The reductive C−O bond cleavage in benzyl alcohols or benzyl ethers[5] and the reduction of azides leading to amines[6] by Me_3SiI have also been observed. However, to the best of our knowledge, there are no precedents for the reductive dehalogenation of aryl halides by Me_3SiI.

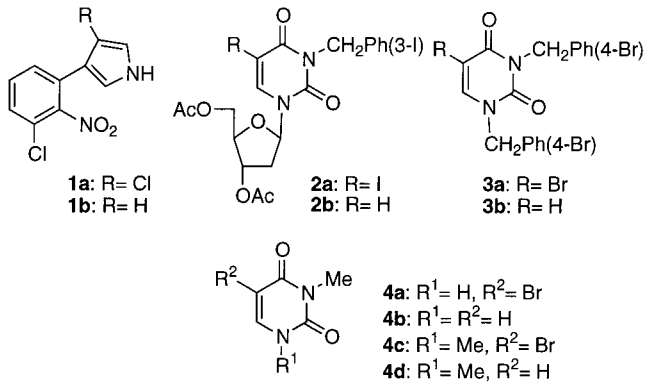

Figure 1.

During the course of our investigations on the chemical modifications of the antifungal chemotherapeutic pyrrolnitrin, 3-chloro-4-(3-chloro-2-nitrophenyl)pyrrole (**1a**), we observed a regioselective reductive dechlorination of **1a** during the reaction with Me_3SiI, providing a simple method for the preparation of 3-(3-chloro-2-nitrophenyl)-pyrrole (**1b**) having a high antifungal activity and, in addition, the first example for the reductive cleavage of heteroaryl C−halogen bonds by Me_3SiI. When the antibiotic **1a** was treated with two equimolar amounts of Me_3SiI in dry chloroform at ambient temperature under an argon atmosphere, the starting **1a** was smoothly consumed and converted into a more polar compound (**1b**), accompanied by a color change from pale yellow to purple and then brown. After stirring for 2 h, TLC densitometric analysis of the reaction mixture showed 10% of remaining **1a** and the formation of a trace amount of an uncharacterized byproduct together with **1b**. UV−visible spectral analysis of the mixture indicated the formation of almost an equimolar amount of iodine (λ_{max}: 510 nm) during the reaction. After treatment of the reaction mixture with sodium thiosulfate to reduce the generated iodine followed by column chromatographic separation, isolation of **1b** in 82% yield as pale yellow crystals occurred. On the basis of its spectral data, the structure of the product **1b** was assigned to 3-(3-chloro-2-nitrophenyl)pyrrole, a previously reported compound without a detailed description of its spectral data.[7]

When the reaction was carried out in deuterochloroform followed by ^1H NMR spectral measurements, an increase in the peak signal assignable to the methyl groups of Me_3SiCl at δ_H 0.44 ppm (δ_C 4 ppm), ac-

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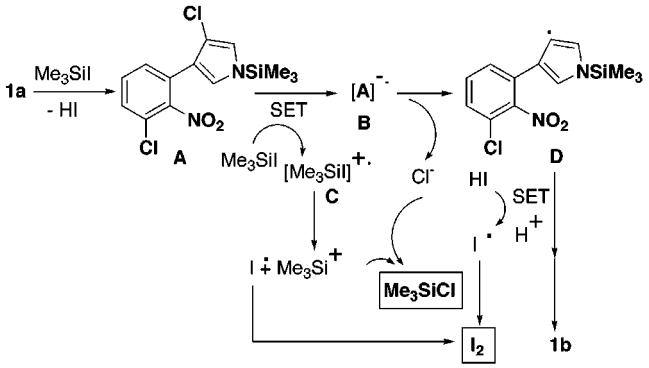
Scheme 1. A Plausible Mechanism for the Dechlorination of 1a by Me_3SiI



companied by a decrease in the peak signal for Me_3SiI at δ_H 0.80 (9H, s) ppm was observed. The formation of Me_3SiCl in this reaction was also proven by GC-MS analysis of the reaction mixture. In further stoichiometry studies, two or more equimolar amounts of Me_3SiI was shown to be required for the complete consumption of the starting **1a**. Employment of bromotrimethylsilane in place of Me_3SiI was not effective for the formation of **1b**, resulting in the almost complete recovery of the starting **1a**.

On the basis of these facts and the chemical reactivity of Me_3SiI,[3] we propose a plausible reaction sequence for the present reductive dechlorination as shown in Scheme 1.[8] The initial step of this reaction should be the N-trimethylsilylation of **1a** leading to an N-protected intermediate **A** accompanied by the generation of hydrogen iodide.[9] A single-electron transfer from Me_3SiI, having a low oxidation potential ($E^{ox}_p = +0.42$V vs. SCE, in dry acetonitrile), to **A** (cf. $E^{red}_{1/2}$ of **1a** $= -1.31$V vs SCE, in dry acetonitrile) results in the formation of a radical anion (**B**), which can release a chloride ion to give a pyrrolyl radical (**D**), accompanying the formation of the Me_3SiI radical cation (**C**). The subsequent reduction of the radical **D** by the generated hydrogen iodide (E^{ox}_p of iodide $= +0.7$ V in acetonitrile)[10] followed by protonation affords the ultimate product **1b**. The chloride ion can be trapped by the radical cation **C** to give Me_3SiCl with release of an iodine atom. The coupling of the generated iodine atoms forms molecular iodine to color the solution purple and then brown.

Characteristics of the present reaction are that the reductive cleavage of the C−Cl bond smoothly and efficiently proceeded even under mild conditions and, in addition, with high chemoselectivity, e.g., the 2-chloronitrobenzene moiety in **1a** was inert under the conditions employed.[11] Analogous dehalogenations were observed in the reactions of 3′,5′-*O*-diacetyl-5-iodo-3-(3-iodobenzyl)-2′-deoxyuridine (**2a**), 5-bromo-1,3-bis(4-bromobenzyl)-1*H*-pyrimidine-2,4-dione (**3a**), and 5-bromo-1*H*-pyrimidine-2,4-diones (**4a,c**), which are susceptible to the single-electron reduction,[12] with Me_3SiI to give the corresponding dehalogenated products, 3′,5′-*O*-diacetyl-3-(3-iodobenzyl)-2′-deoxyuridine (**2b**), 1,3-bis(4-bromobenzyl)-1*H*-pyrimidine-2,4-dione (**3b**), and 1*H*-pyrimidine-2,4-diones (**4b,d**), in moderate yields. Thus, the reductive dehalogenation with Me_3SiI is also applicable to other halogenated heterocycles.

Experimental Section

The melting points are uncorrected. The ^1H and ^{13}C NMR spectra were obtained at 400 and 75 MHz, respectively, using deuterochloroform unless otherwise noted as the solvent. Mass spectra were determined at an ionizing voltage of 70 eV. For the thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (Merck No. 5715; silica gel 60-F_{254}) were used. Column chromatography was performed with silica gel (Merck No. 9385-5B; silica gel 60). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

Reaction of Pyrrolnitrin (1a) with Iodotrimethylsilane (Me_3SiI) or Bromotrimethylsilane (Me_3SiBr). To a solution of **1a** (200 mg, 0.78 mmol) in dry chloroform (80 mL; freshly distilled after the treatment with anhydrous calcium chloride overnight) was added Me_3SiI (97% purity, Aldrich) (323 μL, 2.2 mmol), and the mixture was stirred at ambient temperature under an argon atmosphere for 2 h. TLC densitometric analysis of the reaction mixture showed the formation of a more polar compound as the major product and a trace amount of a less polar uncharacterized product, together with the 10% recovery of the starting **1a**. After treatment with saturated sodium thiosulfate solution (80 mL), the organic solution was well washed with brine (10 mL, two times), dried over anhydrous magnesium sulfate, and evaporated to dryness. The resulting residue was subjected to a silica gel column eluting with toluene to isolate the recovered **1a** (14 mg, 7%) and 3-(3-chloro-2-nitrophenyl)pyrrole (**1b**) (146 mg, 82%): mp 122 °C (lit.[5] mp 121−122 °C); IR (KBr) 3415, 1530, 1378 cm^{-1}; UV (MeCN) 271 (ϵ 8 × 10^3), 207 nm; ^1H NMR δ 6.35 (1H, dd, J = 2 and 4 Hz), 6.82 (1H, dd, J = 3 and 4 Hz), 6.94 (1H, dd, J = 2 and 3 Hz), 7.32 (1H, dd, J = 2 and 8 Hz), 7.37 (1H, t, J = 8 Hz), 7.44 (1H, dd, J = 2 and 8 Hz), 8.42 (1H, br); ^{13}C NMR δ 108, 117, 118, 119, 125, 127, 128, 130 (2), 148; Mass (relative intensity) m/z 224 (M^+ for $C_{10}H_7{}^{37}ClN_2O_2$, 16%), 222 (M^+ for $C_{10}H_7{}^{35}ClN_2O_2$, 52), 197 (32), 195 (100), 166 (22), 149 (24); Anal. Calcd for $C_{10}H_7ClN_2O_2$: m/z 222.0196. Found: m/z 222.0198.

The reaction of **1a** (10.0 mg, 0.04 mmol) with Me_3SiI (5.7 μL, 0.04 mmol) in deuterochloroform (0.4 mL) was followed by measurement of the ^1H and ^{13}C NMR spectra. In these spectra, the increase in the characteristic peak signals (δ_H 0.44 ppm and δ_C 4 ppm) for chlorotrimethylsilane (Me_3SiCl), accompanied by a decrease in the peak signals for Me_3SiI at δ_H 0.80 ppm and δ_C 3 ppm was observed during the reaction. The GC-MS spectrum of the reaction mixture obtained after stirring for 35 min showed the presence of a molecular ion peak (m/z 108) for Me_3SiCl.

After stirring the solution of **1a** (25.6 mg, 0.1 mmol) in dry chloroform (5.0 mL) containing 0.75, 1.0, 1.5, or 2.0 equiv of Me_3-

(8) At this stage, we have no direct evidence strongly supporting the proposed mechanism. The involvement of a single-electron transfer process in this reaction, however, is plausible, taking account of (a) the reasonable redox potentials of the compounds, **1a**, Me_3SiI, and hydrogen iodide; (b) the requirement of two equimolar amounts of Me_3SiI for the complete consumption of the starting halide **1a** in the reaction with Me_3SiI; (c) the formation of almost equimolar amount of the oxidation product, molecular iodine, and the expected Me_3SiCl.

(9) In further experiments carried out according to referees' suggestion, the halogenated compounds, **1a**, **3a**, and **4a**,**c**, were shown to be highly stable in chloroform containing an equimolar amount of hydrogen iodide (57 wt % in distilled water) even after prolonged reaction time (after 1 day), indicating that hydrogen iodide is not the reactive species (at least, in the initial stage) for the present dehalogenation. In the case of the 3′,5′-O-diacetylated nucleoside **2a**, the occurrence of acid hydrolysis leading to the corresponding deacylated product was observed under the conditions employed.

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(11) The treatment of 2-chloro-3-nitropyridine with Me_3SiI under the conditions analogous to the case of **1a** resulted in the reductive dechlorination to give 3-nitropyridine in 41% yield with the 31% recovery of the starting chloronitropyridine. In this reaction, the formation of 3-amino-2-chloropyridine (29%) was also observed. In sharp contrast to these facts, 2-chloronitrobenzene was stable under the conditions employed even after prolonged reaction time (after 1 day).

(12) These 5-bromo-1*H*-pyrimidine-2,4-diones **4a,c** underwent the reductive debromination with ease via a single-electron-transfer process upon treatment with 1-benzyl-1,4-dihydronicotinamide under thermal conditions, see Sako, M.; Hirota, K.; Maki, Y. *Tetrahedron* **1983**, *39*, 3919−3921.

SiI under analogous conditions (for 2 h), TLC densitometric analyses of the reaction mixtures were carried out and showed the formation of **1b** in the following yields: 15% (the remaining of **1a**: 72%) in the case of Me_3SiI (0.75 equiv); 43% (the remaining of **1a**: 45%) in the case of Me_3SiI (1.0 equiv); 77% (the remaining of **1a**: 14%) in the case of Me_3SiI (1.5 equiv); 85% (the remaining of **1a**: 10%) in the case of Me_3SiI (2.0 equiv).

The reaction of **1a** (15 mg, 0.06 mmol) with Me_3SiBr (97% purity, Aldrich) (20 μL, 0.15 mmol) was carried out under the conditions analogous to the case of Me_3SiI. TLC analysis of the reaction mixture showed the formation of a trace amount of **1b** and the almost complete recovery of the starting **1a** in this reaction.

Preparation of 3′,5′-*O*-Diacetyl-5-iodo-3-(3-iodobenzyl)-2′-deoxyuridine (2a). A mixture of 5-iodo-2′-deoxyuridine (98% purity, Aldrich) (361 mg, 1.0 mmol), 3-iodobenzyl bromide (95% purity, Aldrich) (406 mg, 1.3 mmol), and anhydrous potassium carbonate (560 mg, 4.0 mmol) in dry *N*,*N*-dimethylformamide (5 mL) was stirred at ambient temperature overnight. After removal of the precipitate by suction and of the solvent under reduced pressure, the residual oil was purified by column chromatography eluting with chloroform−methanol (30/1) to isolate 5-iodo-3-(3-iodobenzyl)-2′-deoxyuridine (441 mg, 77%): colorless powder; mp 198−199 °C; IR (KBr) 1695, 1654 cm^{-1}; UV (MeOH) 285 (e 6.7 × 10^3), 215 (1.76 × 10^4) nm; ^1H NMR (DMSO-d_6) δ 2.15 (2H, m), 3.53−3.66 (2H, m), 3.80 (1H, dd, J = 3 and 6 Hz), 4.23 (1H, m), 4.96 (2H, t, J = 14 Hz), 5.17 (1H, t, J = 5 Hz), 5.24 (1H, d, J = 4 Hz), 6.11 (1H, t, J = 6 Hz), 7.11 (1H, t, J = 8 Hz), 7.26 (1H, d, J = 8 Hz), 7.62 (1H, d, J = 8 Hz), 7.66 (1H, br s), 8.51 (1H, s); Mass (relative intensity) m/z 570 (M^+, 7%), 454 (M^+ − I, 100). Anal. Calcd for $C_{16}H_{16}I_2N_2O_5$: C, 33.71; H, 2.83; N, 4.91. Found: C, 33.71; H, 3.08, N, 4.88.

A suspension of the benzylated 2′-deoxyuridine (285 mg, 0.5 mmol) in dry pyridine (2 mL) containing acetic anhydride (0.5 mL) was stirred at ambient temperature overnight. After removal of the solvent under reduced pressure, the resulting residual oil was chromatographed over silica gel by elution with chloroform−acetone (50/1) to isolate the desired diacetate **2a** (225 mg, 69%): amorphous powder; mp 68−70 °C; IR (KBr) 1744, 1708, 1660 cm^{-1}; UV (MeOH) 283 (ϵ 8.7 × 10^3), 215 (2.3 × 10^4) nm; ^1H NMR δ 2.11 and 2.20 (each 3H, each s), 2.16 and 2.55 (each 1H, each m), 4.29 (1H, dd, J = 3 and 6 Hz), 4.33 and 4.40 (each 1H, each dd, J = 3 and 12 Hz), 5.08 (2H, t, J = 11 Hz), 5.22 (1H, m), 6.30 (1H, dd, J = 5 and 8 Hz), 7.04 (1H, t, J = 8 Hz), 7.47 (1H, d, J = 8 Hz), 7.62 (1H, d, J = 8 Hz), 7.83 (1H, br s), 7.96 (1H, s); Mass (relative intensity) m/z 654 (M^+, 11%), 610 (2), 455 (13), 454 (21), 201, 140, 81 (100). Anal. Calcd for $C_{20}H_{20}I_2N_2O_7$: C, 36.72; H, 3.08; N, 4.28. Found: C, 36.77; H, 3.30; N, 4.30.

Preparation of 5-Bromo-1,3-bis(4-bromobenzyl)-1*H*-pyrimidine-2,4-dione (3a). To a suspension of 1*H*-pyrimidine-2,4-dione (>98% purity, Tokyo Kasei) (224 mg, 2.0 mmol) and anhydrous potassium carbonate (1.12 g, 8 mmol) in dry *N*,*N*-dimethylformamide (10 mL) was added 4-bromobenzyl bromide (98% purity, Aldrich) (1.27 g, 5.0 mmol), and the mixture was stirred at ambient temperature overnight. After removal of the solvent under reduced pressure, the residue was dissolved into a mixed solvent of ethyl acetate (30 mL) and water (10 mL), and the organic phase was separated, washed with 0.5 N HCl (10 mL) and then brine (10 mL), and evaporated to dryness. The resulting residue was purified by column chromatography eluted with chloroform−acetone (100/1) to isolate 1,3-bis(4-bromobenzyl)-1*H*-pyrimidine-2,4-dione (**3b**) (806 mg, 90%): mp 134−135 °C (from diethyl ether); IR (KBr) 1711, 1663 cm^{-1}; UV (MeOH) 265 (ϵ 9.2 × 10^3), 218 (2.1 × 10^4) nm; ^1H NMR δ 4.85 and 5.07 (each 2H, each s), 5.77 (1H, d, J = 8 Hz), 7.10, 7.14, 7.35, and 7.42 (each 1H, each d, each J = 8 Hz), 7.50 (1H, d, J = 8 Hz); Mass (relative intensity) m/z 452 (M^+ for $C_{18}H_{14}{}^{81}Br_2N_2O_2$, 50%), 450 ($M^+$ for $C_{18}H_{14}{}^{81}Br^{79}BrN_2O_2$, 100), 448 ($M^+$ for $C_{18}H_{14}{}^{79}Br_2N_2O_2$, 50), 281 (21), 279 (21), 238 (25), 236 (25), 212 (8), 210 (8), 171 (49), 169 (51). Anal. Calcd for $C_{18}H_{14}Br_2N_2O_2$: C, 48.03; H, 3.13; N, 6.22. Found: C, 48.00; H, 3.27; N, 6.16.

To a solution of the benzylated pyrimidinedione **3b** (450 mg, 1.0 mmol) in acetic acid (5 mL) was added bromine (62 μL, 1.2 mmol) dropwise, and the mixture was stirred at ambient temperature for 0.5 h. After removal of the solvent under reduced pressure, the residue was dissolved into ethyl acetate (30 mL), and then the solution was washed with brine (10 mL, two times), dried over anhydrous magnesium sulfate, and evaporated to dryness. The resulting residue was purified by column chromatography eluted with chloroform to isolate the desired product **3a** (516 mg, 98%): colorless powder; mp 183−184 °C; IR (KBr) 1705, 1657 cm^{-1}; UV (MeOH) 284 (ϵ 1.14 × 10^4), 219 (2.81 × 10^4) nm; ^1H NMR δ 4.87 and 5.11 (each 2H, each s), 7.16, 7.38, 7.43, and 7.52 (each 1H, each d, each J = 8 Hz), 7.46 (1H, s); Mass (relative intensity) m/z 532 (M^+ for $C_{18}H_{13}{}^{81}Br_3N_2O_2$, 20%), 530 ($M^+$ for $C_{18}H_{13}{}^{81}Br_2{}^{79}BrN_2O_2$, 57), 528 ($M^+$ for $C_{18}H_{13}{}^{81}Br^{79}Br_2N_2O_2$, 57), 526 ($M^+$ for $C_{18}H_{13}{}^{79}Br_3N_2O_2$, 20), 361 (7), 359 (13), 357 (7), 318 (7), 316 (13), 314 (7), 171 (100), 169 (97). Anal. Calcd for $C_{18}H_{13}Br_3N_2O_2$: C, 40.87; H, 2.48; N, 5.30. Found: C, 40.85; H, 2.63; N, 5.29.

Reaction of the 5-Iodo-2′-deoxyuridine Derivative 2a with Me_3SiI. The iodide **2a** (65.4 mg, 0.1 mmol) was treated with Me_3SiI (42.6 μL, 0.3 mmol) in dry chloroform (3 mL) under the conditions analogous to the case of **1a** described above. TLC densitometric analysis of the reaction mixture showed the formation of a more polar compound as the major product, together with the 55% recovery of the starting **2a** (after 2 h). The after-treatment of the reaction mixture in a manner similar to the case of **1a** followed by chromatographic separation eluted with chloroform−acetone (20/1) afforded the recovered **2a** (32 mg) and 3′,5′-*O*-diacetyl-3-(3-iodobenzyl)-2′-deoxyuridine (**2b**) (21 mg, 40%): ^1H NMR δ 2.10 and 2.11 (each 3H, each s), 2.15 and 2.54 (each 1H, each m), 4.26 (1H, dd, J = 3 and 6 Hz), 4.31 and 4.35 (each 1H, each dd, each J = 3 and 12 Hz), 5.01 and 5.05 (each 1H, each d, each J = 14 Hz), 5.21 (1H, m), 5.84 (1H, d, J = 8 Hz), 6.28 (1H, dd, J = 6 and 8 Hz), 7.04 (1H, t, J = 8 Hz), 7.43 (1H, d, J = 8 Hz), 7.45 (1H, d, J = 8 Hz), 7.61 (1H, br d, J = 8 Hz), 7.81 (1H, br s); Mass (relative intensity) m/z 528 (M^+, 48%), 328 (60), 296 (10), 258 (3), 217 (12), 201 (21), 81 (100). Anal. Calcd for $C_{20}H_{21}IN_2O_7$: m/z 528.0393. Found: m/z 528.0402.

Reaction of the 5-Bromopyrimidinedione 3a with Me_3SiI. The bromide **3a** (53.0 mg, 0.1 mmol) was treated with Me_3SiI (42.6 μL, 0.3 mmol) in dry chloroform (3 mL) under the conditions analogous to the case of **2a** described above. TLC densitometric analysis of the reaction mixture showed the formation of the expected **3b** (10%), together with the 74% recovery of the starting **3a** (after 2 h). The structure of the debrominated product **3b** was confirmed by spectral comparison with the authentic compound, after chromatographic separation of the reaction mixture eluted with chloroform-acetone (100/1).

Reaction of 5-Bromo-1*H*-pyrimidine-2,4-diones (4a,c) with Me_3SiI. A suspension of 5-bromo-1*H*-pyrimidine-2,4-dione (**4a**) (19 mg, 0.1 mmol) in dry acetonitrile (10 mL) containing Me_3SiI (29 μL, 0.2 mmol) was stirred at ambient temperature under an argon atmosphere for 2 h. TLC densitometric analysis of the reaction mixture using chloroform−methanol (5/1) as a developing solvent showed the formation of 1*H*-pyrimidine-2,4-dione (**4b**) (7%) in this reaction, accompanied by the recovery of the starting material. The low conversion of this reaction seems to be mainly from the low solubility of the starting **4a** in the employed solvent. The structure of this product was confirmed by the spectral comparison with a commercially available authentic sample after isolation using column chromatographic separation of the reaction mixture.

Analogous results were obtained in the reaction of 5-bromo-3-methyl-1*H*-pyrimidine-2,4-dione (**4c**) (20 mg, 0.1 mmol) with Me_3SiI (29 μL, 0.2 mmol) under similar conditions to afford the expected 3-methyl-1*H*-pyrimidine-2,4-dione (**4d**) in 44% yield.

Supporting Information Available: MS, IR, NMR, and UV spectra for the compounds **1b**, **2a**,**b**, and **3a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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