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REGIOSELECTIVE α–MONOCHLORINATION OF *N*-PROTECTED-3-PIPERIDONES

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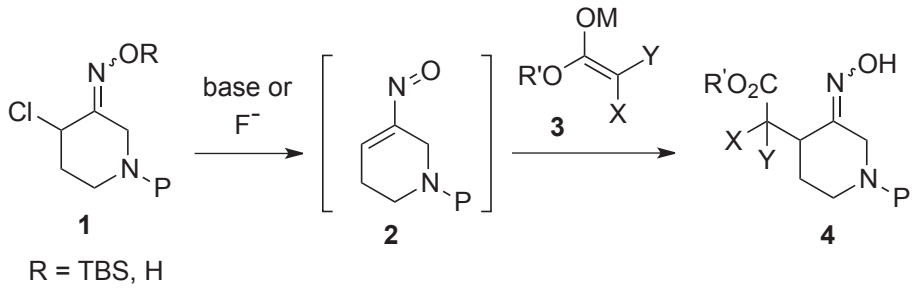
This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday.

Abstract – A direct procedure for regioselective α-monochlorination of various *N*-sulfonyl and *N*-acyl-protected-3-piperidones with *N*-chlorosuccinimide (NCS) and Amberlyst-15 ion exchange resin is reported which leads predominantly (or exclusively) to 4-chloro-3-piperidones in all cases.

INTRODUCTION

As part of our ongoing investigations on utilizing nitrosoalkenes[1] as enolonium ion equivalents[2] in organic synthesis, we have begun to apply what we have learned in our previous studies[3] to the total synthesis of some complex alkaloids. A key reaction in several of these syntheses involves a Michael addition of an ester enolate **3** to a nitrosoalkene **2** generated from the 3-piperidone-derived α-chlorooxime derivative **1** (Scheme 1). In order to synthesize substrates like **1**, we required an efficient route to the

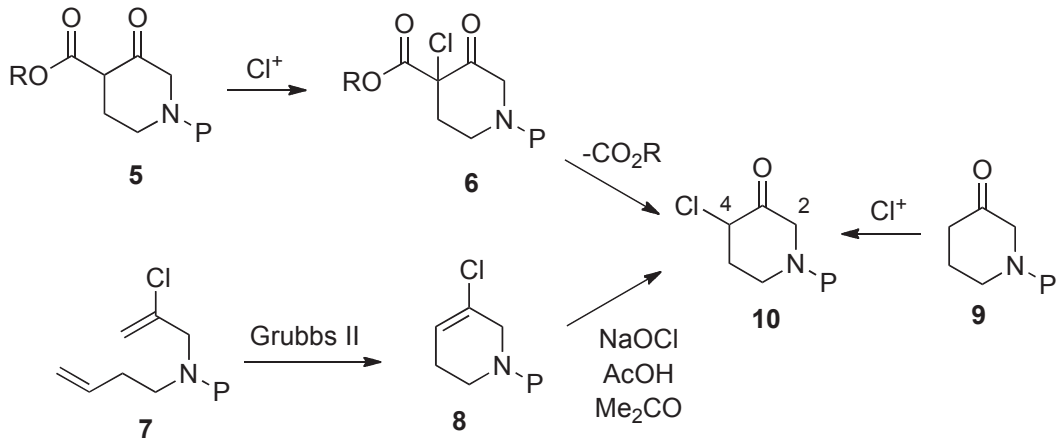


Scheme 1

requisite α-chloroketone precursor **10** (Scheme 2). Several methods are currently available which could be applied in a regioselective synthesis of α-chloroketone **10**.[4] For example, decarboxylation of an

α-chloro-β-ketoester such as **6**,[4a] which may be prepared by the regioselective chlorination of β-ketoester **5**[4a,5] could, in principle, provide 4–chloro-3-piperidone **10**. Alternatively, ring-closing metathesis[6] of chlorodiene **7** and subsequent oxidation[4b] of vinyl chloride **8** with sodium hypochlorite in AcOH/acetone could lead to α-chloroketone **10** in a regioselective manner. We have, in fact, examined both of these strategies for construction of the desired 4-chloro-3-piperidones without success.

Since we planned on utilizing α-chloroketone **10** as an early intermediate in our synthetic endeavors and required gram quantities of this material, we desired a straightforward strategy that would avoid multiple synthetic steps and/or expensive catalysts/reagents. The most attractive approach for the synthesis of α-chloroketones like **10** would be a direct α-chlorination of a suitably *N*-protected-3-piperidone **9** to yield the 4-chloro regioisomer (Scheme 2). In this regard, we were encouraged by several reports on the monobromination of α-aminoketone derivatives with Br_2 to produce α'-bromo-α-aminoketones as the major regioisomer.[7] Research from the Merck labs has revealed that treating *N*-protected-3-piperidones (protecting group = SES or Cbz) or 3-piperidone hydrobromide with Br_2 produces the corresponding 4-bromo-3-piperidones with good regioselectivity.[7a,8] Interestingly, Overman and coworkers have found that subjecting either *N*-tosyl- or *N*-Boc-3-piperidone to a free radical bromination (NBS, AIBN in refluxing CCl_4) leads to exclusive formation of the corresponding 2-bromo derivatives.[9] In contrast, only a few examples exist on the regioselective α-chlorination of ketones containing an α-nitrogen substituent and, to the best of our knowledge, none of these systems involve a 3-piperidone derivative.[7c]



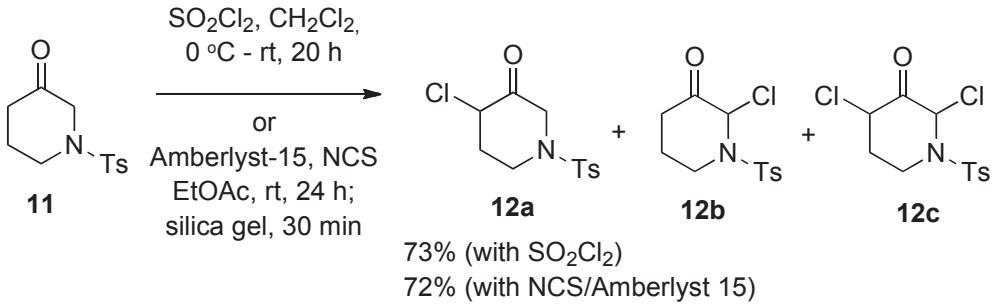
Scheme 2

RESULTS AND DISCUSSION

Since treatment of *N*-protected-3-piperidones with molecular bromine affords primarily 4-bromo-3-piperidones,[7a] we sought to develop an analogous α-chlorination procedure. However, a process which avoided the use of chlorine gas was highly desireable. We were therefore prompted to examine sulfuryl chloride as a chlorinating reagent since Masilamani and Rogic have shown this

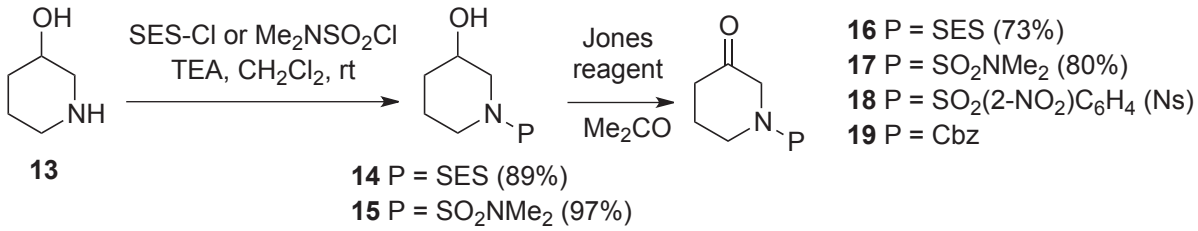
compound to be effective for the mono-α-chlorination of cyclohexanones.[10] We were pleased to find that treatment of *N*-tosyl-3-piperidone (**11**) with fresh sulfuryl chloride (1.1 equiv) produced a mixture of α-chloroketones (~5-7:1 **12a**:**12b** based on proton NMR analysis of the crude reaction mixture) favoring the desired 4-chloro-3-piperidone **12a** (Scheme 3). In this particular case, separation of the 2-chloro and 4-chloro-regioisomers can be achieved *via* column chromatography to afford the desired 4-chloro-3-piperidone **12a** in 73% isolated yield. However, when this procedure was repeated using older samples of sulfuryl chloride (~1 month to 1 year stored at room temperature), an excess of sulfuryl chloride (3-8 equiv) was required in order for the reaction to go to completion.[11] Although, using excess reagent did not appear to affect the overall yield or regioselectivity of this reaction, we were prompted to examine alternative electrophilic chlorinating procedures that would give more predictable and reproducible results.

After some experimentation, we have found that treatment of *N*-tosyl-3-piperidone (**11**) with NCS (1.5 equiv) and Amberlyst-15 ion exchange resin (H^+ form) in EtOAc at room temperature,[12] followed by silica gel column chromatography, provided a ~4.2:1 ratio of the the 4-chloro derivative **12a** and an inseparable mixture of the 2-chloro isomer **12b** along with the dichloro compound **12c** (~2:1 **12b**:**12c** based on ^{1}H NMR analysis). Interestingly, the crude product mixture from this chlorination has a very complex proton NMR spectrum apparently due to the presence of a large amount of the enol tautomers. However, stirring this material with silica gel prior to column chromatography converts most of the enol to the keto form.[13] The desired α-chloroketone **12a** was isolated in pure form in 72% yield *via* this procedure, essentially the same as in the chlorination with sulfuryl chloride.



Scheme 3

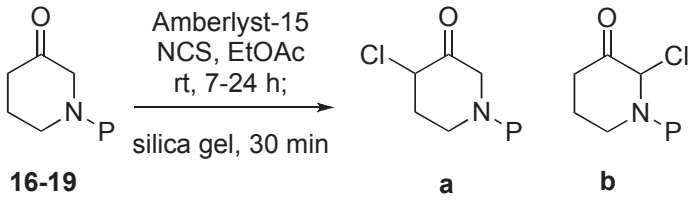
To explore the generality of this chlorination protocol, we have prepared a series of *N*-protected-3-piperidones to examine using the above NCS-based procedure (Scheme 4). Thus, ketones **16**[14] and **17** were prepared by *N*-sulfonylation of 3-hydroxypiperidine (**13**), followed by Jones oxidation of the resulting alcohols **14** and **15**. Known ketones **18** and **19** were acquired in a similar manner according to literature procedures.[7a,15]



Scheme 4

We were pleased to find that the *N*-sulfonyl- and *N*-acyl-protected-3-piperidones examined using the NCS/Amberlyst-15 chlorination conditions produced the corresponding 4-chloro-3-piperidones with good or complete regioselectivity (Table 1).[13] In two cases, small amounts of the 2-chloro isomers were

Table 1. Regioselective α-Chlorination of *N*-Protected-3-piperidones



entry	ketone	ratio (a:b)[a]	isolated yield (%)[b]
1	**16**	7:1[c]	65
2	**17**	10:1[c]	77
3	**18**	3.5:1	67[e]
4	**19**	--[d]	67

[a]Ratio of regioisomers of chromatographically isolated products. Ratios for impure minor isomers determined by NMR integration
[b]Isolated yields for the major monochlorination products **16-19a**
[c]2-Chloro isomer could not be obtained in pure form
[d]4-Chloro isomer only product isolated
[e]Minor isomer **18b** isolated pure in 19% yield (see Experimental)

detected (entries 1 and 3). The major 4-chloropiperidones could be isolated in pure form in good yields *via* flash column chromatography. It should also be noted that *N*-alkyl-3-piperidones tend to be rather unstable and therefore we have not investigated chlorination reactions involving this type of system.[16]

In summary, we have developed a reliable, reproducible method for synthesis of various protected 4-chloro-3-piperidones which we expect will be useful intermediates in synthesis of both nitrogen heterocycles and alkaloids.

EXPERIMENTAL

General Experimental Procedures. Ethyl acetate was purchased from EMD Chemicals and was used without further purification. Amberlyst-15 and sulfuryl chloride were purchased from Aldrich and employed as obtained. Flash column chromatography was performed using EM Science silica gel 60 (230-400 mesh). ^{1}H and ^{13}C NMR spectra were obtained on a Bruker CDPX-300, DPX-300, or DRX-400 MHz spectrometer. Nominal mass spectra were obtained on an Applied Biosystems 150EX. High resolution mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer.

Chlorination of *N*-tosyl-3-piperidone (11) with sulfuryl chloride. To a stirred solution of 3-piperidone **11** (300 mg, 1.18 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added fresh sulfuryl chloride (0.11 mL, 1.3 mmol) and the solution was stirred for 20 h, gradually warming to rt. An aqueous solution of $NaHCO_3$ was added and the resulting mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (2:2:1 hexanes/CH_2Cl_2/EtOAc) to yield α-chloroketone **12a** (249 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.35 (t, *J* = 5.0 Hz, 1H), 3.84 (s, 2H), 3.53-3.50 (m, 1H), 3.42-3.38 (m, 1H), 2.53-2.48 (m, 4H), 2.27-2.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 145.0, 132.9, 130.5, 128.1, 58.6, 53.5, 42.3, 34.0, 22.0; LRMS-ES+ *m/z* (relative intensity) 288 (MH^+, 100); HRMS-ES+ ($C_{12}H_{18}ClN_2O_3S$) calcd 305.0729 ($M+NH_4^+$), found 305.0727.

1-((2-(Trimethylsilyl)ethyl)sulfonyl)piperidin-3-ol (14). To a stirred solution of 3-hydroxypiperidine (**13**, 871 mg, 8.44 mmol) and TEA (2.35 mL, 16.9 mmol) in CH_2Cl_2 at 0 °C was added SES-Cl[17] (1.60 mL, 8.44 mmol). The resulting solution was stirred for 2 h at 0 °C and then concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (1:1:1 hexanes/CH_2Cl_2/EtOAc) to yield 3-hydroxypiperidine **14** (2.02 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90-3.80 (m, 1H), 3.55 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.40-3.34 (m, 1H), 3.20-3.10 (m, 1H), 3.03 (dd, *J* = 12.2, 7.2 Hz, 1H), 2.90-2.84 (m, 2H), 2.44 (d, *J* = 4.9 Hz, 1H), 1.90-1.85 (m, 2H), 1.66-1.51 (m, 2H), 1.03-0.97 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.1, 52.7, 46.8, 46.5, 32.3, 23.0, 10.4, -1.6; HRMS-ES+ ($C_{10}H_{24}NO_3SSi$) calcd 266.1246 ($M+H^+$), found 266.1241.

3-Hydroxy-*N*,*N*-dimethylpiperidine-1-sulfonamide (15). To a stirred solution of 3-hydroxypiperidine (**13**, 2.0 g, 19.77 mmol) and TEA (5.52 mL, 39.5 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added *N*,*N*-dimethylsulfamoyl chloride (2.12 mL, 19.77 mmol). The resulting solution was stirred for 2 h at 0 °C and 2 h at rt. The reaction mixture was then concentrated *in vacuo* to give a residue which was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to yield 3-hydroxypiperidine **15** (4.0

g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58-3.52 (m, 2H), 3.38-3.34 (m, 1H), 3.21-3.16 (m, 1H), 2.80-2.67 (m, 1H), 2.63-2.60 (m, 7H), 1.74-1.61 (m, 2H), 1.42-1.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.0, 52.9, 46.6, 38.4, 32.4, 22.9; HRMS-ES+ ($C_7H_{20}N_3O_3S$) calcd 226.1255 ($M+NH_4^+$), found 226.1233.

1-((2-(Trimethylsilyl)ethyl)sulfonyl)piperidin-3-one (16). To a stirred solution of 3-hydroxypiperidine **14** (2.02 g, 7.61 mmol) and acetone (30 mL) at rt was added Jones reagent (2.5 M, 3.35 mL). The resulting solution was stirred at rt for 1 h, *i*-PrOH (0.8 mL) was added and the reaction mixture was stirred for an additional 5 min. The resulting slurry was filtered through a plug of glass wool washing with acetone. The filtrate was concentrated *in vacuo* to give a residue which was taken up in $NaHCO_{3\ (aq)}$ and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, and then dried over $MgSO_4$. Concentration of the organic layers *in vacuo* gave a residue which was purified by flash column chromatography on silica gel (2:2:1 hexanes/CH_2Cl_2/EtOAc) to give ketone **16** (1.47 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2H), 3.50 (t, J = 5.3 Hz, 2H), 2.90-2.84 (m, 2H), 2.49 (t, J = 6.5 Hz, 2H), 2.06-2.00 (m, 2H), 0.99-0.93 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 55.8, 47.3, 44.7, 38.6, 24.1, 10.4, -1.6; HRMS-ES+ ($C_{10}H_{25}N_2O_3SSi$) calcd 281.1355 ($M+NH_4^+$), found 281.1373.

***N*,*N*-Dimethyl-3-oxopiperidine-1-sulfonamide (17).** To a stirred solution of 3-hydroxypiperidine **15** (4.00 g, 19.2 mmol) and acetone (60 mL) at rt was added Jones reagent (2.5 M, 8.45 mL). The resulting solution was stirred for 1 h, *i*-PrOH (10 mL) was added and the reaction mixture was stirred for an additional 5 min. The resulting slurry was filtered through a plug of glass wool washing with acetone. The filtrate was concentrated *in vacuo* to give a residue which was taken up in $NaHCO_{3\ (aq)}$ and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers where washed with water, brine, and dried over $MgSO_4$. Concentration of the organic layers *in vacuo* gave a residue which was purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to give ketone **17** (3.15 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 2H), 3.42 (t, J = 5.8 Hz, 2H), 2.78 (s, 6H), 2.45 (t, J = 6.9 Hz, 2H), 2.06-2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 56.5, 45.4, 38.7, 38.4, 23.7; HRMS-ES+ ($C_7H_{15}N_2O_3S$) calcd 207.0803 ($M+H^+$), found 207.0804.

General procedure for chlorination of *N*-protected-3-piperidones with NCS and Amberlyst-15. To a stirred solution of 3-piperidone (0.80 mmol) in EtOAc (12 mL) was added Amberlyst-15 (300 mg) followed by NCS (158 mg, 1.18 mmol) and the resulting mixture was stirred until the starting material was consumed as monitored by tlc (~7-24 h). Silica gel (~ 1 g) was added and the resulting mixture was stirred for an additional 30 min, filtered, and concentrated *in vacuo* to give a residue, which was purified by flash column chromatography on silica gel using a mixture of hexanes/CH_2Cl_2/EtOAc to afford the α-chloroketone. Isolated yields of the products are shown in Table 1.

4-Chloro-1-((2-(trimethylsilyl)ethyl)sulfonyl)piperidin-3-one (16a). ^{1}H NMR (300 MHz, $CDCl_3$ + 1 drop of trifluoroacetic acid to generate the ketone[13]) δ 4.59 (t, *J* = 6.0 Hz, 1H), 4.20 (ABq, *J* = 48.6, 16.0 Hz, 2H), 3.82-3.64 (m, 2H), 3.11-3.05 (m, 2H), 2.68-2.60 (m, 1H), 2.38-2.31 (m, 1H), 1.09-0.95 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 58.3, 53.0, 48.9, 42.2, 34.8, 10.1, -2.3; LRMS-ES+ *m/z* (relative intensity) 298 (MH^+, 30); HRMS-ES+ ($C_{10}H_{24}N_2O_3SClSi$) calcd 315.0965 ($M+NH_4^+$), found 315.0957.

4-Chloro-*N*,*N*-dimethyl-3-oxopiperidine-1-sulfonamide (17a). ^{1}H NMR (300 MHz, $CDCl_3$ + 1 drop of trifluoroacetic acid) δ 4.57-4.53 (m, 1H), 4.18-3.84 (m, 2H), 3.80-3.56 (m, 2H), 2.88-2.83 (m, 6H), 2.68-2.62 (m, 1H), 2.37-2.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 58.7, 53.8, 43.0, 38.4, 31.2.

4-Chloro-1-((2-nitrophenyl)sulfonyl)piperidin-3-one (18a). ^{1}H NMR (300 MHz, $CDCl_3$ + 1 drop of trifluoroacetic acid) δ 8.14-8.04 (m, 1H), 7.86-7.71 (m, 3H), 4.57-4.51 (m, 1H), 4.33-4.02 (m, 2H), 3.85-3.74 (m, 2H), 2.65-2.58 (m, 1H), 2.38-2.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 148.3, 135.2, 132.8, 131.7, 131.2, 125.2, 58.5, 53.0, 42.2, 34.3; LRMS-ES+ *m/z* (relative intensity) 319 (MH^+, 50); HRMS-ES+ ($C_{11}H_{15}N_3O_5SCl$) calcd 336.0421 ($M+NH_4^+$), found 336.0411.

2-Chloro-1-((2-nitrophenyl)sulfonyl)piperidin-3-one (18b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.05 (m, 1H), 7.77-7.67 (m, 3H), 5.12 (s, 1H), 3.75-3.51 (m, 2H), 2.81-2.69 (m, 1H), 2.38-2.30 (m, 1H), 2.11-2.03 (m, 1H), 1.88-1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 148.3, 134.6, 132.9, 132.4, 131.2, 124.9, 87.2, 64.7, 40.7, 35.6.

Benzyl 4-Chloro-3-oxopiperidine-1-carboxylate (19a). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of carbamate rotamers) δ 7.50-7.30 (m, 5H), 5.28-5.17 (m, 2H), 4.49-4.35 (m, 1H), 4.25-3.82 (m, 2H), 3.54-3.45 (m, 1H), 2.55-2.46 (m, 1H), 2.29-1.79 (m, 1H), 1.28-1.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 155.2, 136.3, 136.2, 129.0, 128.8, 128.6, 128.5, 128.3, 68.6, 68.3, 59.3, 59.2, 52.5, 49.9, 46.0, 41.2, 40.3, 39.5, 38.0, 35.6, 34.1.

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