Rearrangements in the Reduction of 3-Iodobicyclo[1.1.1]pentyl Azide with Lithium Aluminum Hydride: Mechanistic Evidence of Intermediates

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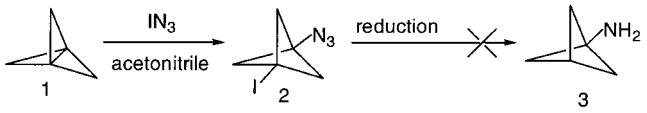
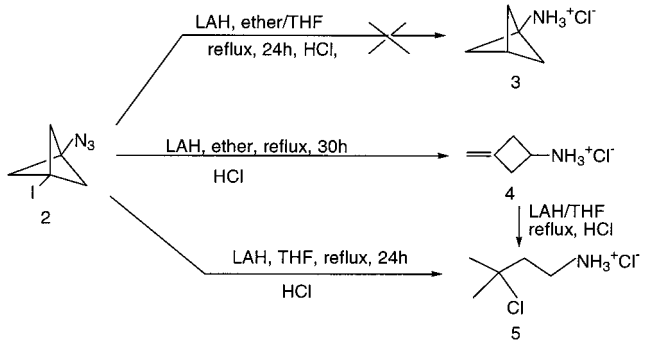
Pseudohalogens add to olefins to afford α,β addition products.[1] Iodine azide, bromine azide, and iodine isocyanate provide α,β iodoazide, bromoazide, and iodoisocyanate, respectively. Because of the nitrogen functionality these compounds play an important role in the synthesis of amines, amino acids, aziridines, or other nitrogen derivatives. [1.1.1]Propellane (**1**), the smallest tricyclic bridgehead compound, possesses its highest electron density at the bridgehead carbons and undergoes addition reactions at the 1,3 position.[2] We have conducted addition reactions of [1.1.1]propellane with pseudohalogen iodine azide (IN_3),[3,4] which provided 3-iodobicyclo-[1.1.1]pentyl azide in a 92% yield. It was hoped that reduction of **2** would lead to 1-bicyclo[1.1.1]pentylamine (**3**), a compound needed for other purposes.Attempts to convert 3-iodobicyclo[1.1.1]pentyl azide to 1-bicyclo[1.1.1]-pentylamine employed a wide variety of reducing agents. The main concern was to keep the [1.1.1]pentyl skeleton intact since this moiety is highly strained,[5,6] and both the iodine and azide are susceptible to reduction. Both azide and iodine at bridgehead positions are not generally known to be reduced although 3-chloroadamantyl azide has been reduced to adamantylamine.[7] 1-Bicyclo[1.1.1]-pentylamine has shown greater activity than a *tert*-butyl group[8] in the 1-position of quinilone against Gram-positive and Gram-negative bacteria as well as anaerobic organisms. The successful reduction of 3-iodobicyclo-[1.1.1]pentyl azide to 1-bicyclo[1.1.1]pentylamine can eliminate several steps in comparison with the synthesis from 1-bicyclo[1.1.1]pentyl carboxylic acid.[2,9] However, all the efforts for reduction to afford 1-bicyclo[1.1.1]pentylamine failed. We were surprised to obtain an unexpected open chain 3-chloro-3-methylbutylamine hydrochloride in up to 72% yield from reduction of **2** with lithium aluminum hydride in THF.

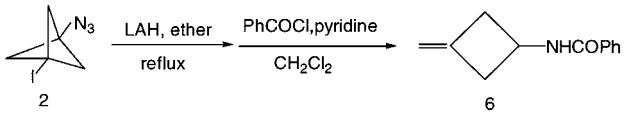
Scheme 1



Scheme 2



Scheme 3



Diborane is known to be a mild reducing agent and is effective in partial reduction of *o*-bromobenzoic acid to *o*-bromobenzyl alcohol.[10] Other reducing agents such as n-tributyltin hydride, triethylsilane, lithium in liquid ammonia, sodium in ethanol, magnesium in methanol, zinc and hydrochloric acid, samarium iodide, and alkaline earth metal reductions are also effective for partial reduction.[11] However, reduction of 3-iodobicyclo[1.1.1]-pentyl azide with these reagents afforded starting materials or unknown fragmentation products.In ether, reduction with LAH under mild conditions and at a low temperature afforded 3-methylenecyclobutylamine hydrochloride after hydrogen chloride workup in 82% yield. 3-Methylenecyclobutylamine hydrochloride with LAH in THF under more vigorous conditions yielded 86% of 3-chloro-3-methylbutylamine hydrochloride.

Neither of the free amines of **4** and **5** could be isolated directly due to their volatility. However, after the aqueous workup from the reduction with LAH in ether, the amide from benzoyl chloride and pyridine was obtained in a 74% yield.Reduction of 2 with diborane under mild reaction conditions yielded 3-iodobicyclo[1.1.1]pentylamine (**7**) and 3-iodobicyclopentylamine hydrochloride (**8**) with hydrogen chloride. These are supported by IR, and H^1 and C^{13} NMR, although the microanalysis of these compounds were off. However, the reduction of 3-iodobicyclo[1.1.1]pentylamine hydrochloride with LAH in ether afforded 3-methylenecyclobutylamine hydrochloride (**4**). Further reduction of **4** in THF under vigorous

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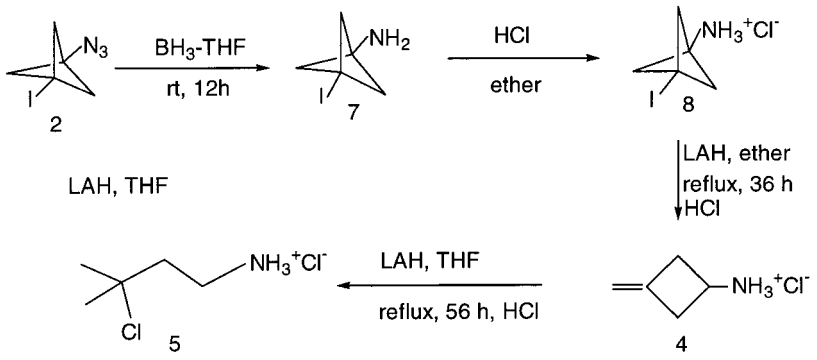
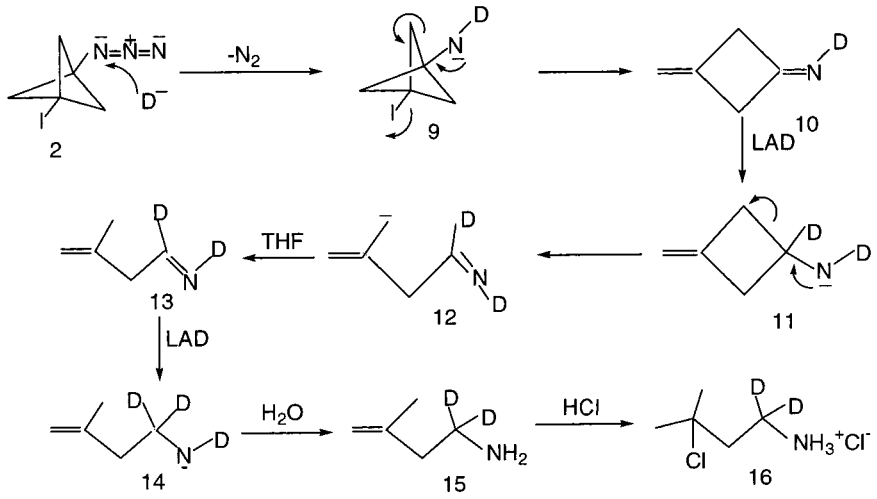
Scheme 4



Scheme 5



condition and with hydrogen chloride provided 3-chloro-3-methylbutylamine hydrochloride (**5**), implying that the borane did reduce 3-iodobicyclo[1.1.1.]pentyl azide to 3-iodobicyclo[1.1.1]pentylamine.To understand the mechanism of formation of 3-chloro-3-methylbutylamine hydrochloride, we conducted the reduction of the 3-iodobicyclo[1.1.1]pentyl azide with lithium alumunium deuteride (LAD) under identical conditions. In ether, the reduction afforded 74% of 1-deutero-3-methylenecyclobutylamine hydrochloride, and in THF, 71% of 3-chloro-1,1-dideutero-3-methylbutylamine hydrochloride.

On the basis of these observations, we propose the formation of 3-chloro-3-methylbutylamine hydrochloride as shown in Scheme 5.

Experimental Section

General. THF and ether were distilled from sodium and benzophenone. Acetonitrile was distilled from phosphorus pentoxide, pyridine from potassium hydroxide, and dichloromethane from calcium sulfate. All the solvents after distillation were preserved under either 4A molecular seive or potassium hydroxide and used with a positive pressure of nitrogen. All other reagents used were purchased from Aldrich Chemical Co., Milwaukee, WI.

IR spectra were recorded on Perkin-Elmer 1600 Seris FT-IR and Magna-IR 550 instruments. ^{1}H and ^{13}C NMR spectra were obtained on a Varian-Gemini 300 MHz or a Varian Unity 400 MHz (75 or 100 MHz for ^{13}C, respectively) spectrometer where chemical shifts are reported in parts per million referenced to TMS (0.00 ppm) and chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C). Melting points were determined in an open capillary tube on a Unimelt or a Meltemp apparatus and are uncorrected. TLC was performed using silica gel 60 F (E. Merck, Darmstadt, Germany), and flash column chromatography was performed on ICN silica (32-62, 60 A from ICN Biomedicals Gmbh, Germany). Elemental analysis and HRMS were performed by Atlantic Microlab Inc., Norcross, GA, and Iowa State University of Science and Technology II.

[1.1.1]Propellane.[2] [1.1.1]Propellane was prepared by the Wiberg procedure[2] incorporating the Lynch−Daily modification for synthesis of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane.[12] The yield of [1.1.1]propellane was estimated to be 60% by the reaction with a solution of iodine in carbon tetrachloride.

Synthesis of 3-Iodobicyclo[1.1.1.]pentyl Azide (2). To a stirred slurry of 2.40 g (36.92 mmol) sodium azide in 30 mL of acetonitrile in a salt−ice bath (temp −15 to −20 °C) was added slowly 3.0 g (18.48 mmol) of iodine monochloride over a period of 15 to 20 min under positive pressure of argon. A yellow-orange color was formed within 10 min from the dark color of iodine monochloride. The mixture was stirred for 10 min. An ethereal solution of 18.52 mmol [1.1.1]propellane was then added slowly with a syringe over a 15−20 min period. At the end of the addition, the yellow-orange color turned to a pale yellow. The salt−ice bath was removed, and the mixture was stirred at room temperature for 18 h. The pale yellow slurry was poured into 100 mL water, and the mixture was extracted with ether (3 × 25 mL). The combined ethereal solution was washed with 5% sodium thiosulfate (100 mL), to remove unreacted iodine, and water (500 mL) and dried with anhydrous magnesium sulfate. Removal of the solvent under vacuum left a light orange liquid. TLC in pentane indicated a mixture of two compounds. Separation was done under flash chromatography (silica gel) with pentane as an eluent. The first eluent after evaporation afforded a white solid. Recrystallization from *n*-pentane gave 0.4 g, 7% 1,3-diiodobicyclo[1.1.1]pentane, as white crystals, mp 145−146 °C (dec). ^{1}H NMR ($CDCl_3$) δ 2.67 (s, 6H); ^{13}C NMR δ 68.1 ($3CH_2$), −1.8 (2C); HRMS calcd for $C_5H_6I_2$: 319.85590; found 319.85542.

The second fraction, after vacuum evaporation of the eluent at room temperature, gave an orange oil 4.01 g, 92%, 3-iodobi-

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cyclo[1.1.1]pentyl azide (**2**). IR (neat) cm^{-1} 2919 and 2109; ^1H NMR ($CDCl_3$) δ 2.43 (s, 6H); ^{13}C NMR δ 61.3 (CH_2), 55.1 (CN_3), −2.9 (CI); HRMS calcd for C_5H_6NI: 206.95450; found 206.95456 (parent $C_5H_6N_3I - N_2$, as no parent ion was observed under EI conditions).

Reduction of 3-Iodobicyclo[1.1.1]pentyl Azide. (a) With lithium Aluminum Hydride in Ether. 3-Methylenecyclobutylamine Hydrochloride (4). To a stirred slurry of 0.28 g (7.0 mmol) of lithium aluminum hydride in 15 mL of dry ether under positive pressure of argon was added dropwise 0.718 g (3.06 mmol) 3-iodobicyclo[1.1.1.]pentyl azide in 5 mL of dry ether. The mixture was refluxed gently for 16 h and cooled to room temperature. The unreacted hydride was taken up with 15 mL of ice-cooled water. Ether (15 mL) was added to the solution, and two layers separated. The aqueous layer was extracted with ether (3 × 20 mL), and the combined ether was dried with anhydrous magnesium sulfate overnight and filtered. Dry hydrogen chloride gas was passed over the filtrate for 1 min. Immediately, white amine salt formed. Evaporation of the solvent provided a white solid which was recrystallized from ethanol−ethyl acetate to give 0.30 g, 82%, of 3-methylenecyclobutylamine hydrochloride (**4**), mp 174−175 °C. IR (KBr) cm^{-1} 3343, 3000, 2729; ^1H NMR (D_2O) δ 4.85 (b, s, $=CH_2$), 3.76 (m, CH), 2.99 (m, 2H), 2.78 (m, 2H); ^{13}C NMR (D_2O) δ 140.0, 108.6, 41.8, 36.8. Anal. Calcd for C_5H_9NCl: C, 50.20, H, 8.44, N, 11.71; found: C, 50.19, H, 8.44, N, 11.63.

(b) With Lithium Aluminum Hydride in THF. 3-Chloro-3-methylbutylamine Hydrochloride (5). To a 100 mL three-neck flask equipped with a condenser, 20 mL addition funnel, magnetic stirrer, and a stopper under positive pressure of argon was added 0.37 g (9.75 mmol) of lithium aluminum hydride and 25 mL of dry THF. The reaction flask was cooled by an ice−water bath, and 1.03 g (4.40 mmol) 3-iodobicyclo[1.1.1]pentyl azide was added to the addition funnel in 10 mL of dry THF. The 3-iodobicyclo[1.1.1]pentyl azide solution was added drop by drop to the stirred slurry over 25 min. The ice−water bath was removed, and it was stirred at room temperature for 6 h. The reaction mixture was then refluxed gently for 24 h and cooled to room temperature. The unreacted lithium aluminum hydride was destroyed with ice-cold water (15 mL). Ether (15 mL) was added to the solution, and two layers were separated. The aqueous layer was extracted with ether (4 × 25 mL). The combined ether layers were dried over anhydrous magnesium sulfate and filtered. Dry hydrogen chloride gas was passed over the filtrate for 1 min. A white salt formed immediately. Evaporation of the ether under vacuum gave 3-chloro-3-methylbutylamine hydrochloride (**5**), as a white powder. Recrystallization from ethanol−ethyl acetate provided needlelike crystals, 0.60 g, 86%, mp 194−195 °C. ^1H NMR (DMSO) δ 8.05 (b, 3H), 2.91 (t, 2H), 2.03 (t, 2H), 1.55 (s, 6H); ^{13}C NMR (DMSO) δ 70.1, 42.3, 35.8, 32.3. Anal. Calcd for $C_5H_{13}NCl_2$: C, 38.98, H, 8.31, N, 8.86. Found: C, 38.77, H, 8.30, N, 8.88.

Reduction at Low Temperature. When the addition of 3-iodobicyclo[1.1.1.]pentyl azide was done at −15 to −20° C in either ether or THF (reaction is not dependent on solvents at this low temperature) and stirred at the same temperature for 2 h and 6h at room temperature, the same product, 3-methylenecyclobutylamine hydrochloride (**4**). was obtained. The mp and the spectroscopic data confirm the compound to be **4**.

3-Methylenecyclobutylbenzamide (6). To a stirred slurry of 0.28 g (7.37 mmol) of lithium aluminum hydride in 15 mL of ether was added slowly 0.73 g (3.11 mmol) 3-iodobicyclo[1.1.1]-pentyl azide in 5 mL of ether. The mixture was refluxed gently for 24 h, cooled to room temperature, and treated with ice-cooled water (15 mL). Ether (15 mL) was added, and two layers separated. The aqueous layer was extracted with ether (3 × 20 mL), the combined ether was dried over anhydrous magnesium sulfate and filtered. The filtrate was reduced to approximately 15 mL under flow of nitrogen gas and transferred to a 50 mL three-neck flask equipped with a condenser, magnetic stirrer, calcium chloride drying tube, and rubber septum. Pyridine (4.89 g, 61.82 mmol) was added to the solution via a syringe and stirred for 10 min. Benzoyl chloride (0.51 g, 3.63 mmol) was added slowly to the solution for 5 min and stirred for 7 h. Evaporation of the solvent and excess pyridine under reduced pressure gave a pale orange solid which was dissolved in 30 mL of $CHCl_3$, washed with 20% HCl (100 mL) and then with 100 mL of water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a white powder. Recrystallization from ethanol−water (50:50) gave white crystals of **6**, 0.43 g, 74%, mp 142−143 °C. IR (K Br) cm^{-1} 3310, 1636, 1540, 1491, 1345, 1304, 892;^1H NMR ($CDCl_3$) δ 7.40−7.82 (m 5H), 6.55 (s, b, 1H), 4.88 (m, 2H), 4.61 (m, 1H), 3.16 (m, 2H), 2.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.1, 142.1, 134.4, 131.4, 128.5, 126.9, 107.3, 41.3, 40.5. Anal. Calcd for $C_{12}H_{13}NO$; C, 76.96, H, 7.01, N, 7.48. Found: C, 76.96, H, 6.97, N, 7.47.

Reduction of 3-Methylenecyclobutylamine Hydrochloride. To stirred slurry of 0.1 g (2.63 mmol) of lithium aluminum hydride in 15 mL of THF under positive pressure of argon was added slowly 0.15 g (1.20 mmol) of solid 3-methylene cyclobutylamine hydrochloride (**4**) for 20 min. The mixture was refluxed for 48 h and cooled to room temperature. The unreacted lithium aluminum hydride was taken up with ice-cooled water (10 mL), and 10 mL ether was added. The two layers were separated, and the aqueous layer was extracted with ether (3 × 15 mL). The combined ether layers were dried over anhydrous magnesium sulfate and filtered. The salt precipitated when dry hydrogen chloride gas was passed over the filtrate for 1 min. The amine hydrochloride was recrystallized from ethanol−ethyl acetate as white crystals 0.09 g, 51%, 3-chloro-3-methylbutylamine hydrochloride (5), mp 194−195° C. Proton and carbon spectra NMR confirmed the structure of the compound.

Reduction of 3-Iodobicyclo[1.1.1]pentyl Azide. (a) With LAD in Ether. 1-Deutero-3-methylenecyclobutylamine Hydrochloride. To a stirred slurry of 0.450 g (10.72 mmol) of lithium aluminum deuteride in 25 mL of dry ether under an argon atmosphere was added slowly 0.91 g (3.86 mmol) of 3-iodobicyclo[1.1.1]pentyl azide in 5 mL of dry ether. The reaction mixture was refluxed for 24 h and cooled to room temperature. The mixture was taken up with 15 mL of ice-cooled water. The organic layer was extracted with ether (3 × 15 mL), dried overnight with anhydrous magnesium sulfate, and filtered. Dry hydrogen chloride gas was passed over the filtrate for 1 min. A white precipitate of salt formed immediately. Evaporation of the ether gave a white salt which was recrystallized from ethanol to give pure crystals, 0.34 g, 74%, 1-deutero-3-methylenecyclobutylamine hydrochloride, mp 191−193 °C. ^1H NMR (D_2O) δ 4.85 (m, 2H), 3.00 (d, 2H), 2.76 (d, 2H); ^{13}C NMR (D_2O) δ 135.5, 104.0, 36.9, 32.2.

The addition of **2** to the slurry of LAD at −15 to 20 °C and stirred at room temperature for 12 h in ether gave the same compound.

(b) With LAD in THF. 3-Chloro-1,1-dideutero-3-methylbutylamine Hydrochloride (16). To a stirred slurry of 0.456 g (23.10 mmol) of lithium aluminum deuteride in 20 mL of THF under argon atmosphere was added slowly 0.97 g (4.13 mmol) of 3-iodobicyclo[1.1.1]pentyl azide. The reaction mixture was refluxed for 48 h and cooled to room temperature. The lithium aluminum deuteride was taken up with ice-cold water (15 mL), and 15 mL of ether was added. The organic layer was extracted with ether (3 × 20 mL), dried over anhydrous magnesium sulfate, and filtered. Dry hydrogen chloride gas was passed over the filtrate, and the amine hydrochloride precipitate formed. The precipitate was separated by filtration and recrystallized from ethanol−ethyl acetate to a pure white salt, 0.46 g, 71%, 3-chloro-1,1-dideutero-3-methylbutylamine hydrochloride (**16**), mp 194−196 °C. ^1H NMR (D_2O) δ 1.66 (s, 2H) and 1.08 (s, 6H).

Reduction of 1-Deutero-3-methylenecyclobutylamine Hydrochloride with LAD in THF. To a stirred slurry of 0.2 g (4.76 mmol) of lithium aluminum deuteride under argon atmosphere in 15 mL of dry THF was added 0.20 g (1.65 mmol) of 1-deutero-3-methylenecyclobutylamine hydrochloride slowly over 10 min. The reaction mixture was refluxed for 24 h and cooled to room temperature. The excess lithium aluminum deuteride was taken up with ice−water and dried over anhydrous magnesium sulfate. The magnesium sulfate was separated by filtration. Dry hydrogen chloride gas was passed over the filtrate. The salt was filtered and purified by recrystallization from ethanol−ethyl acetate to afford a pure amine salt **16**, 0.17 g, 64%. Proton and carbon spectra confirmed that the salt was 3-chloro-1,1-dideutero-3-methylbutylamine hydrochloride (**16**).

Synthesis of 3-Iodobicyclo[1.1.1]pentylamine (7). To a stirred solution of 0.55 g (2.34 mmol) of 3-iodobicyclo[1.1.1]pentyl azide in 10 mL of dry THF equipped with a condenser and rubber

septum under positive pressure of argon was added 3 mL (3 mmol) of 1 M diborane−THF complex dropwise for 10 min. The reaction mixture was stirred for 24 h and cooled in an ice−water bath. Ice-cold water (5 mL) was added slowly to destroy excess borane, and the reaction mixture was allowed to reach room temperature. The aqueous layer was saturated with 2 g of potassium carbonate. The organic layer was extracted with ether (3 × 15 mL) and dried over anhydrous magnesium sulfate. TLC in methylene chloride−*n*-pentane (1:1) indicated a mixture of two compounds. Evaporation of solvent under reduced pressure gave a white powder. The powder was dissolved in methylene chloride (2 mL) and purified by silica gel flash chromatography with dichloromethane/*n*-pentane (1:1) as an eluent. The first fraction was collected as 0.06 g of a colorless oil which could not be identified by proton NMR. The second fraction after evaporation of eluent gave a white powder 0.34 g, 70%, 3-iodo-bicyclo-[1.1.1]pentylamine (**7**), mp 104−106 °C. IR (KBr), cm^{-1}, 3342, 3248 (d), 2907, 2401, 1443, 1184; ^1H NMR (DMSO) δ 2.20 (s, 6H); ^{13}C NMR (DMSO) δ 60.7 (CH_2), 59.4 (CN), 1.6 (CI).

When dry hydrogen chloride gas was passed over the second fraction of the eluent, a white precipitate of salt was formed. Evaporation of the solvent gave the amine salt which was purified by recrystallization from ethyl acetate to 0.36 g, 62%, mp 139−140 °C, 3-iodobicyclo[1.1.1]pentylamine hydrochloride (**8**). IR (KBr) cm^{-1}, 3338, 3013, 2449, 1692, 1539, 1252, 1190, 967; ^1H NMR (D_2O) δ 2.40 (s, 6H); ^{13}C NMR (D_2O) δ 61.5 ($3CH_2$), 49.0 (C−N), −2.6 (C−I).

Analytical analyses on **7** and **8** were unsatisfactory but reduction of **8** with LAH gave **4** thus implying the correct structure for **8**.

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