Novel Formation of 2-Arylquinolines and 1,3-Benzoxazines from 2-(1-Alkenyl)acylanilides and Active Halogens

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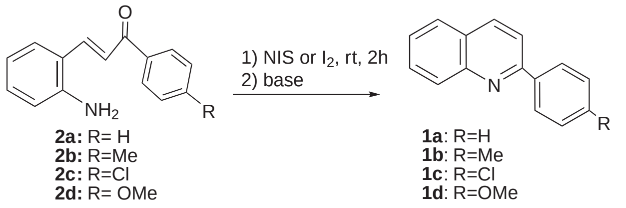
2-Arylquinolines **1** were obtained in good yields by reacting iodine or NIS with 2-aminochalcones **2**, which were easily synthesized by the Claisen–Schmidt reaction from 2-nitrobenzaldehyde and acetophenones. The reaction of iodine with 2-isopropenylacetanilide (**3a**), followed by the addition of aq. $NaHCO_3$, afforded 4-iodomethyl-2,4-dimethyl-4*H*-3,1-benzoxazine (**6a**), of which the structure has previously been reported to be 1-acetyl-2-iodomethyl-2-methyl-1,2-dihydrobenzazete (**4a**) or 1-acetyl-3-iodo-3-methylindoline (**5a**). The reaction mechanism is discussed.

Quinolines **1** are widely occurring natural alkaloids that display a variety of pharmacological activities, including anesthetic, tumoricidal, antihypertensive, and antibacterial.[1] The development of new synthetic methods for quinoline derivatives is in great demand, because of the increased resistance of malarial parasites to chloroquine, a hitherto used malarial drug.[2] One of the important methods is the photoisomerization of 2-aminochalcones **2** to afford 2-substituted quinolines.[3] If *cis–trans* isomerization occurs by halogen activation of **2**, 2-substituted quinolines **1** will form. Recently, iodine- or *N*-iodosuccinimide (NIS)-activated intramolecular cyclizations of 2-(1-alkenyl)acylanilides **3** have been achieved by Kobayashi et al. and Arisawa et al., but with different results, namely, formation of 1,2-dihydrobenzazetes **4** by Kobayashi et al.[4] and indolines **5** by Arisawa et al.,[5] has been observed. These results prompted us to investigate the correct structures of the products obtained from the reaction of 2-(1-alkenyl)acylanilides **3** with active halogen compounds. Herein, we report the novel synthesis of 2-arylquinolines **1** and 3,1-benzoxazines **6** from 2-alkenylanilides and 2-aminochalcones.

Results and Discussion

Synthesis of 2-Arylquinolines. Since the intramolecular cyclization that uses iodine and 2-alkenylanilide **3** has been proven to be a good procedure for the synthesis of indoles[6] and **5**,[5] we applied it to the synthesis of quinolines **1** via intramolecular cyclization of 2-aminochalcone **2**. The synthesis of 2-aminochalcones **2** was carried out by reacting acetophenones with 2-nitrobenzaldehyde according to the reported procedure.[7] When 2-aminochalcone (**2a**) was treated with NIS (equimolar amount) at rt followed by the addition of aq. $NaHCO_3$, 2-phenylquinoline (**1a**) was obtained in 80% yield (Scheme 1).

To improve the yield of **1a**, the reaction conditions, including solvent, temperature, and reaction time, were varied (Table 1). Treatment of **2a** with iodine (1.2 molar amount) in the presence of solid $NaHCO_3$ at rt for 1 h resulted in the formation of the same compound **1a** in 85% yield. When the reaction with NIS (1.2 molar amount) at 0 °C was carried out, **1a** was obtained in 88% yield (Entry 3). In contrast, quinoline **1a** was not obtained when *N*-chlorosuccinimide

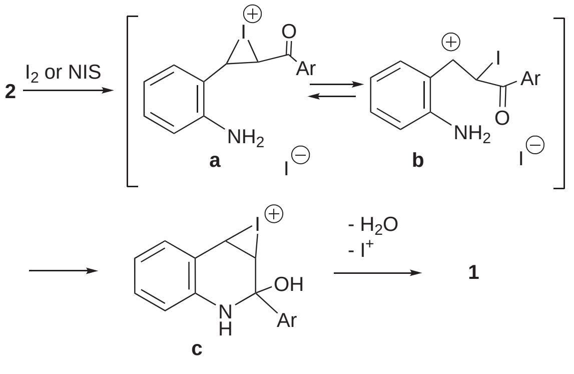


Scheme 1.

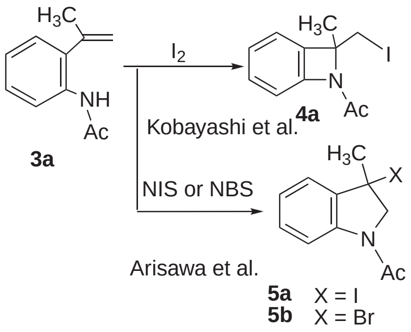
Table 1. Reaction of 2-Aminochalcones **2** with Active Halogens

Entry		R	Halogen	Mol. Amt.	Solvent	Time/h	Temp	Product	Yield/%
1	**2a**	H	NIS	1	CH_2Cl_2	2	rt	**1a**	80
2	**2a**	H	I_2	1.2	CH_2Cl_2	2	rt	**1a**	85
3	**2a**	H	NIS	1.2	CH_3CN	2	0 °C	**1a**	88
4	**2a**	H	NBS	1.2	CH_2Cl_2	5	rt	**1a**	0
5	**2a**	H	NCS	2	CH_2Cl_2	12	rt	**1a**	0
6	**2a**	H	I_2	2	CH_2Cl_2	12	0 °C	**1a**	88
7	**2b**	Me	I_2	1.2	CH_2Cl_2	rt	0 °C	**1b**	83
8	**2c**	Cl	I_2	1.2	CH_2Cl_2	rt	0 °C	**1c**	82
9	**2d**	OMe	I_2	1.2	CH_2Cl_2	rt	0 °C	**1d**	93

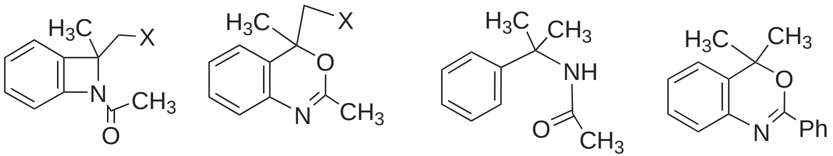
Published on the web September 13, 2007; doi:10.1246/bcsj.80.1824



Scheme 2.



Scheme 3.



4a: X = I
4d: X = SCH_3

6a: X = I
6d: X = SCH_3

7

8

Chart 1.

(NCS) or *N*-bromosuccinimide (NBS) was used (Entries 4 and 5). Thus, the intramolecular cyclization of **2** by using active iodine was achieved.

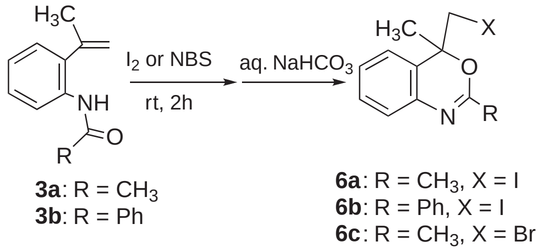
The reaction might proceed through iodonium ion intermediate **a**. Owing to the co-existence of cation **a** and benzyl cation **b**, a conformational change should result in the formation of intramolecular cyclization adduct **c**, from which quinoline **1** is afforded after iodonium ion abstraction and dehydration (Scheme 2).

The present method has a number of advantages over photoisomerization,[3] because workup was very simple. The reaction mixture could be filtered, followed by evaporation of the solvent to give almost pure **1** (see experimental section).

Synthesis of 3,1-Benzoxazines. The reaction of 2-isopropenylacetanilide (**3a**) with iodine or NIS has been reported by Kobayashi et al.[4] and Arisawa et al.,[5] respectively. The reaction of **3a** with iodine gave 1-acetyl-2-iodomethyl-2-methyl-1,2-dihydrobenzazete (**4a**),[4] whereas the reaction with NIS or NBS gave 1-acetyl-3-iodo-3-methylindoline (**5a**) or 1-acetyl-3-bromo-3-methylindoline (**5b**), respectively (Scheme 3).[5]

We were interested in the difference in reactivity between iodine and NIS (or NBS) toward 2-isopropenylacetanilide **3a**. As the reported spectral data of **4a** and **5b** were quite similar, we performed these reactions under conditions similar to those reported by Kobayashi et al.[4] and Arisawa et al.[5] Unfortunately, the spectral data of **5a** was not reported by Arisawa et al. Treatment of **3a** with iodine (3 molar amounts) and $NaHCO_3$ in acetonitrile at 0 °C resulted in the formation of pale yellow crystals, the spectral data of which were identical with those of **4a**, reported by Kobayashi et al. The reaction of **3a** with NBS in dichloromethane, followed by the addition of sat. $NaHCO_3$, gave colorless crystals, the mp and spectral data of which were identical with those of **5b**, reported by Arisawa et al. On the other hand, the reaction of **3a** with NIS, followed by the addition of sat. $NaHCO_3$, according to the procedure by Arisawa et al., afforded pale yellow crystals (**5a** by Arisawa et al.), the spectral data of which were identical with those of **4a**, reported by Kobayashi et al. These results clearly showed the need to reinvestigate the exact structures of these products. Three possible structures were examined: dihydrobenzazete **4a**, proposed by Kobayashi et al.; indoline **5a** or **5b**, suggested by Arisawa et al.; and 4-iodomethyl-2,4-dimethyl-4*H*-3,1-benzoxazine (**6a**). We first examined 2,3-dihydroindole **5b**. The ^{1}H NMR spectrum of **5b** showed methylene doublet signals at 3.50 and 3.67 ppm, and methyl signals at 1.80 and 2.17 ppm. The methylene carbon signal at 40.2 ppm in the ^{13}C NMR spectrum of **5b** resonated at a higher field than the methylene signal of 1-benzoyl-3-(1-hydroxy-1-methylethyl)indoline (52.4 ppm).[8] Additionally, the amide carbonyl carbon signal at 159.5 ppm resonated at a higher field than normal amide signals (165–175 ppm), suggesting that the structure of **5** is incorrect. Then, we analyzed the structure of dihydrobenzazetes **4a** by comparing the IR and ^{1}H NMR data of **4a** and **6a** with those of *N*-1-methyl-1-phenylethylacetamide (**7**)[9] and 2-phenyl-4,4-dimethyl-4*H*-3,1-benzoxazine (**8**) (Chart 1).[10]

The IR spectra of **4a**, **7**, and 2-methyl-4,5-dihydrooxazole showed strong absorptions at 1645 (C=O), 1650 (C=O), and 1665 cm^{-1} (C=N), which cannot be used to differentiate three structures. The ^{1}H NMR spectrum of **4a** showed methylene doublet signals at 3.39 and 3.58 ppm, and methyl signals at 1.81 and 2.17 ppm. The ^{1}H NMR spectrum of **8** showed 4-methyl signal at 1.71 ppm, while that of **7** showed an acetyl group at 1.95 ppm. These data again showed the difficulty in determining the exact structure. However, the signal at 159.4 ppm for **4a** in the ^{13}C NMR spectrum would be too high for an acetamide carbonyl carbon (168.8 ppm for **7**). In comparison, the signal assigned to the iminyl carbon at the 2-position of 3,1-benzoxazine **8** resonated at δ 156.7, which was comparable to the value for **4a**. More definitive information was given by the chemical shift of the signal due to the quaternary carbon at the 4-position of **4a**, which resonated at δ 77.3, similar to that of the corresponding carbon of 2-phenyl-2-propanol



Scheme 4.

Table 2. Reaction of **3** with Active Halogens

Substrate	Halogen	equiv	Solvent	Product	Yield/%
3a	I_2	1.5	CH_3CN	**6a**	86
3a	NIS	1.1	CH_2Cl_2	**6a**	91
3b	I_2	1.2	CH_2Cl_2	**6b**	92
3b	NBS	1.2	CH_2Cl_2	**6c**	88

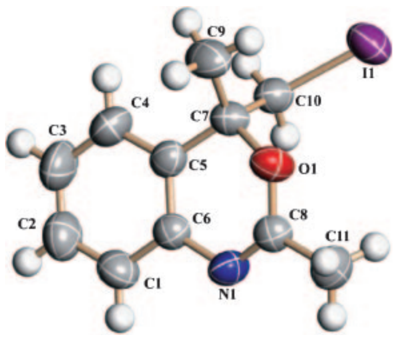
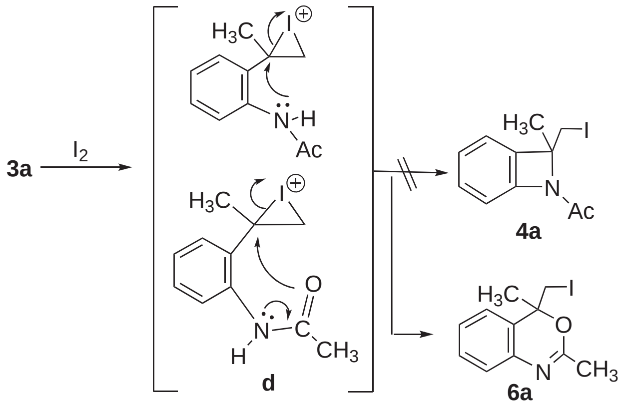


Fig. 1. ORTEP drawing of 3,1-benzoxazine **6a**. Selected bond lengths and angles. Bond length: C6–N1 1.421(6) Å, N1–C8 1.265(7) Å, C8–O1 1.346(7) Å, C7–O1 1.460(7) Å, C5–C6 1.392(7) Å, C5–C7 1.523(8) Å. Bond Angle: O1–C7–C5 110.1(4)°, N1–C8–O1 126.3(5)°, C8–O1–C7 120.4(4)°, C5–C6–N1 121.3(5)°, C6–C5–C7 118.8(5)°, C6–N1–C8 118.0(4)°.

(δ 72.4). Additionally, as the C=N carbon of 2-phenyl-4*H*-3,1-benzoxazine resonated at 157.4 ppm,[11] we concluded that the exact structure of this compound should not be 1,2-dihydrobenzazete **4a** but 4*H*-3,1-benzoxazine **6a**. The reaction of anilide **3a** with NBS at rt, followed by the addition of aq. $NaHCO_3$, also gave colorless crystals of **6c** (Scheme 4).

The results are shown in Table 2. Recently, we have reported the reaction of 2-isopropenylacetanilide (**3a**) with dimethylmethylthiosulfonium trifluoromethanesulfonate to afford 1-acetyl-2-methyl-2-methylthiomethyl-1,2-dihydrobenzazete (**4d**), which should be corrected to 2,4-dimethyl-4-methylthiomethyl-4*H*-3,1-benzoxazine (**6d**).[12]

Since the recrystallization of **6a** from hexane–dichloromethane (5:1) gave single crystals, X-ray crystallographic analysis of **6a** was carried out. Figure 1 shows an ORTEP drawing of **6a**. The results clearly show that activated intermediate **d** is attacked by acyl oxygen at the benzyl position, which is more cationic than the β-position, to afford not 1,2-dihydrobenzazetes **4a** but the less strained six-membered heterocycle, 4*H*-3,1-benzoxazine **6a** (Scheme 5).



Scheme 5.

In summary, we developed a simple method for the synthesis of 2-phenylquinolines and 4*H*-3,1-benzoxazines, using iodine or NIS as double-bond activating reagents, which resulted in the intramolecular cyclization of 2-alkenylanilides. Thus, the regioselective and chemoselective syntheses of 3,1-benzoxazines **6** and quinolines **1** were achieved by the use of 2-alkenylanilides and active halogen compounds.

Experimental

General. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography (TLC) was performed on commercially available pre-coated aluminum plates (Merck silica Kieselgel 60F254). All solvents were distilled before use, and no further treatment was carried out. NMR spectra were measured on a Varian Innova-400 (400 MHz for ^1H, 100 MHz for ^{13}C). The melting points were not corrected.

Materials. 2-Nitrobenzaldehyde, acetophenones, and 2-isopropenylaniline were commercially available. Aminochalcones **2a–2d** were synthesized by the reported procedure.[7] 2-Isopropenylanilides **3a** and **3b** were synthesized by the reported procedure.[13]

Reaction of 2a with NIS. To a solution of **2a** (112 mg, 0.50 mmol) in dichloromethane (5 mL) was added NIS (124 mg, 0.55 mmol) in one portion at rt. After stirring for 2 h, the reaction mixture was washed with aq $NaHCO_3$ (10%), separated, and dried over magnesium sulfate, and the solvent was evaporated to give pale brown crystals of **1a**, which was chromatographed over silica gel by eluting with dichloromethane–hexane (1:1) to afford colorless crystals of **1a** (82 mg, 0.40 mmol). Recrystallization from dichloromethane–hexane gave pure **1a**. mp 83–84 °C: Spectral data of **1a** was identical with the commercially available sample (mp 84–85 °C).

Reaction of 2-Aminochalcone with Iodine. To a solution of **2a** (56 mg, 0.25 mmol) in acetonitrile (3 mL) containing $NaHCO_3$ (21 mg, 0.25 mmol) was added iodine (76 mg, 0.30 mmol) in one portion. After stirring for 1 h at 0 °C, the reaction mixture was washed with 10% $Na_2S_2O_3$ and extracted with dichloromethane (5 mL × 3), separated, and dried over magnesium sulfate, and the solvent was evaporated to give pale brown crystals of 2-phenylquinoline (**1a**), which was recrystallized from dichloromethane–hexane to afford pure **1a** (43 mg, 0.21 mmol). 2-*p*-Tolylquinoline (**1b**) was obtained in a similar manner by using **2b** (95 mg, 0.40 mmol) and iodine (121 mg, 0.48 mmol). **1b** (77 mg, 0.35 mmol): mp 80–81 °C (lit.[14] 81–82 °C).

2-*p*-Chlorophenylquinoline (**1c**) was obtained in a similar manner by using **2c** (77 mg, 0.30 mmol) and iodine (91 mg, 0.36

mmol). **1c** (62 mg, 0.26 mmol): mp 110–111 °C (lit.[15] mp 112–114 °C).

2-*p*-Methoxyphenylquinoline (**1d**) was obtained in a similar manner by using **2d** (76 mg, 0.30 mmol) and iodine (91 mg, 0.36 mmol). **1d** (64 mg, 0.27 mmol): mp 120–121 °C (lit.[14] mp 120–122 °C).

Reaction of 2-Isopropenylacetanilide (3a) with Iodine. To a solution of **3a** (88 mg, 0.50 mmol) in acetonitrile (5 mL) containing $NaHCO_3$ (126 mg, 1.5 mmol) was added iodine (381 mg, 1.50 mmol) in one portion. After stirring for 1 h at 0 °C, the reaction mixture was washed with aq. 10% $Na_2S_2O_3$ and aq. 10% $NaHCO_3$ and extracted with dichloromethane (5 mL × 3), separated, and dried over magnesium sulfate, and the solvent was evaporated to give colorless crystals of 4-iodomethyl-2,4-dimethyl-4*H*-3,1-benzoxazine (**6a**), which was chromatographed over silica gel by eluting with dichloromethane to afford pure **6a** (129 mg, 0.43 mmol). Colorless plates; mp 67–69 °C (dichloromethane–hexane 5:1) (lit.[4] mp 70–72 °C as **4a**); IR (neat) 3004, 2945, 1638 (C=N), 1598, 1579, 1480, 1448, 1422, 1373, 1293, 1264, 1196, 1150, 1029, 978, 883, 767 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (s, 3H, Me), 2.17 (s, 3H, =C–CH_3), 3.39 (d, 1H, $J = 11.2$ Hz, CH_2), 3.58 (d, 1H, $J = 11.2$ Hz, CH_2), 7.08 (d, 1H, $J = 8.0$ Hz, Ar), 7.09–7.20 (m, 2H, Ar), 7.29 (dd, 1H, $J = 1.6$ Hz and 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 16.48 (CH_3), 22.11 (CH_3), 26.75 (CH_2), 77.57 (q-C), 123.19 (Ar), 124.87 (Ar), 126.61 (Ar), 126.81 (Ar), 129.65 (Ar), 138.47 (Ar), 159.75 (N=C).

4-Iodomethyl-4-methyl-2-phenyl-4*H*-3,1-benzoxazine (**6b**): Colorless plates; mp 97–100 °C (dichloromethane:hexane = 4:1) (lit.[4] mp 98–101 °C as dihydrobenzazete); IR (neat) 3052, 2997, 2941, 1622 (C=N), 1597, 1572, 1481, 1446, 1373, 1317, 1261, 1244, 1198, 1160, 1092, 1067, 1028, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (s, 3H, CH_3), 3.49 (d, 1H, $J = 11.2$ Hz, CH_2), 3.67 (d, 1H, $J = 11.2$ Hz, CH_2), 7.18 (d, 1H, $J = 8.0$ Hz, Ar), 7.23 (m, 1H, Ar), 7.33–7.52 (m, 5H, Ar), 8.25 (dd, 2H, $J = 7.2$ Hz and 2.0 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 16.03 (CH_3), 26.85 (CH_2), 77.74 (q-C), 123.30 (Ar), 125.82 (Ar), 127.06 (Ar), 128.52 (Ar), 128.62 (Ar), 129.74 (Ar), 131.84 (Ar), 132.48 (Ar), 139.07 (Ar), 156.31 (N=C).

Reaction of 3a with NBS. To a solution of **3a** (88 mg, 0.50 mmol) in dichloromethane (5 mL) was added NBS (97 mg, 0.55 mmol) in dichloromethane (5 mL) in one portion. After stirring for 2 h at rt, the reaction mixture was washed with 10% $NaHCO_3$ and extracted with dichloromethane (5 mL × 3), separated, dried over magnesium sulfate, and filtered, and the solvent was evaporated to give colorless crystals of 4-bromomethyl-2,4-dimethyl-4*H*-3,1-benzoxazine (**6c**), which was recrystallized from dichloromethane–hexane to afford pure **6c** (111 mg, 0.44 mmol). Colorless plates, mp 84–86 °C (dichloromethane:hexane = 4:1) (lit.[5] mp 86–87 °C as **5b**); IR (neat) 3009, 2954, 1638 (C=N), 1598, 1580, 1481, 1448, 1426, 1373, 1296, 1267, 1240, 1208, 1162, 1051, 1025, 983, 896, 853 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.49 (d, 1H, $J = 11.2$ Hz, CH_2), 3.67 (d, 1H, $J = 11.2$ Hz, CH_2), 7.09 (d, 1H, $J = 8.0$ Hz, Ar), 7.13–7.21 (m, 2H, Ar), 7.31 (dd, 1H, $J = 8.0$ and 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 21.62 (CH_3), 25.35 (CH_3), 40.23 (CH_2), 77.95 (q-C), 123.12 (Ar), 124.59 (Ar), 126.42 (Ar), 126.78 (Ar), 129.72 (Ar), 138.67 (Ar), 159.80 (N=C).

X-ray crystallographic data for **6a**: Crystal data for $C_{11}H_{12}$-INO. Colorles plate. Crystallized from hexane–dichloromethane (5:1). Mo Kα radiation. $M_r = 301.11$, $a = 9.7558(8)$ Å, $b = 11.6392(10)$ Å, $c = 10.6851(8)$ Å, $V = 1164.03(16)$ Å^3, $T = 296$ K, monoclinic, space group: $P2_1/n$, $S = 1.01$, $Z = 4$. 4225 independent reflections, $R = 0.0352$ for 2241 reflections ($I < 2\sigma(I)$), $wR = 0.1073$, $S = 1.01$, $R_{int} = 0.0221$. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-643239 for **6a**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/reterieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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