An Efficient Synthesis of Substituted 4-Aryl-3-Cyano-2-Amino Thiophenes by a Stepwise Gewald Reaction

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The title compounds were efficiently synthesised starting from aryl methyl ketones in 3 steps. Knoevenagel condensation of aryl methyl ketones with malononitrile gave the corresponding crotonitriles (5a-f). Methyl groups of the crotonitriles (5a-f) were then efficiently brominated by refluxing and lightening the reaction media to give bromocrotonitriles (6a-f). The bromocrotonitriles (6a-f) were finally cyclised by treatment with NaSH to give the title compounds.

Key Words: Aminothiophenes, bromocrotonitriles, substituted aminothiophenes.

Introduction

Highly substituted thiophenes (1) form an internal part of numerous natural products and pharmaceuticals. They are often used as novel conducting polymers and as isosteric replacements for phenyl groups in medicinal chemistry. The electronic and optical properties of polythiophene and its derivatives have been the subject of many papers. Azo dyes with heterocyclic diazo components led to commercial products to replace the conventional azobenzene disperse dyes. Some derivatives of 2 obtained from the coupling moieties of 2-aminothiophenes and 2-aminothiazoles were distinguished by their high colour strength and brilliant shades.

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Since the first reported preparation of 2-aminothiophene\textsuperscript{20}, the synthesis of highly functionalised aminothiophenes has been extensively studied.\textsuperscript{21} There are 4 main synthetic approaches for 2-aminothiophenes, 3 of which utilise pre-existing thiophene rings, namely the reduction of nitro/\textsuperscript{22}/nitroso groups,\textsuperscript{23} rearrangements of carboxyclic acid derivatives\textsuperscript{24,25}, and nucleophilic displacements of mercapto/\textsuperscript{26}/iodo groups\textsuperscript{27} with amines. The other method includes ring closure reactions from non-thiophene starting materials, and is less developed for the preparation of simple 2-aminothiophenes (Gewald reaction, Scheme 1).\textsuperscript{28–31}

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{CN} & \\
\text{ylide-nitrile} & \quad \xrightarrow{\text{S}} & \quad \text{Ph} \\
\text{NHEt$_2$} & \quad \text{ethanol} & \quad \text{aminothiophene} \\
X = \text{COOR; C(O)NH$_2$; CN}
\end{align*}
\]

\textbf{Scheme 1.} Gewald reaction

In this study, we report an improved synthesis of the 3,4-disubstituted-2-aminothiophenes (9a-f) by a stepwise Gewald reaction.

\textbf{Experimental Section}

\textbf{General.} Melting points were determined on a Büchi model 530 apparatus and are uncorrected. Infrared spectra were recorded on a Mattson model 1000 FT-IR spectrometer. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on a 200 (50) MHz spectrometer. The mass spectra were recorded on Finnigan GC-MS instruments. Column chromatography was performed on silica gel (60-200 mesh) and activated alumina (70-230 mesh) from Merck Co. TLC was carried out on Merck 0.2 mm silica gel 60 F$_{254}$ analytical aluminium plates.

\textbf{The preparation of crotonitriles 5a-f; typical procedure}\textsuperscript{32}

To a stirred solution of acetophenone (3a) (5.8 g, 0.048 mol) in 50 mL of dry and freshly distilled benzene were added ammonium acetate (6.96 g, 0.090 mol) and malononitrile 4 (3.2 g, 0.048 mol). The reaction mixture was refluxed for 6 h (3b, 3c, 3e and 3f: 12 h, 3d: 8 h), and then cooled to room temperature. After the solvent was removed, the residue was diluted with water. The organic phase was extracted with ether (3
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x 50 mL). The combined solutions were washed with water (2 x 10 mL) and dried over MgSO₄. After removal of the solvent, the residue was recrystallised from CHCl₃ to give 2-(1-Phenyl-ethylidene)-malononitrile (5a) (6.4 g, 79%).

2-(1-Phenyl-ethylidene)-malononitrile (5a): (79%; from CHCl₃/Hexane, colourless crystals, mp 92 °C). (Lit32. 92 °C).¹³C NMR: (50 MHz, CDCl₃)δ 177.39, 137.94, 134.25, 131.12, 129.34, 114.77, 114.71, 86.80, 26.27.

2-(1-Naphthalen-1-yl-ethylidene)-malononitrile (5b): (82%; from CHCl₃/Hexane, colourless crystals, mp 72-73 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.95 (m, 2H, ArH), 7.42-7.35 (m, 5H, ArH), 2.74 (s, 3H, CH₃) ¹³C NMR (50 MHz, CDCl₃): δ 179.97, 136.56, 135.19, 134.50, 131.06, 130.66, 130.35, 129.86, 129.45, 129.25, 125.44, 115.01, 114.89, 86.68, 27.87. IR (KBr film): 3062, 3021, 2235, 1588, 1513, 1429, 1371, 1260, 1177, 1025 cm⁻¹. EIMS m/z (%): 218 (M⁺, 100), 203(64), 190(82), 176(21), 152(20), 128(19). Anal. calc. For C₁₅H₁₀N₂: C, 82.55; H, 4.62; N, 12.84. Found C, 82.67; H, 4.65; N, 12.64.

2-(1-Naphthalen-2-yl-ethylidene)-malononitrile (5c): (85%; yellow crystals, mp 106-107 °C). ¹H NMR (200 MHz, CDCl₃): δ 8.09 (bs, 1H, ArH), 7.98-7.55 (m, 6H, ArH), 2.74 (s, 3H, CH₃) ¹³C NMR (50 MHz, CDCl₃): δ 177.21, 136.74, 135.19, 134.50, 131.06, 130.66, 130.35, 129.86, 129.45, 129.25, 125.44, 115.01, 114.89, 86.68, 26.29. IR (KBr film): 3050, 2225, 1630, 1562, 1500, 1465, 1373, 1288, 1176, 1014 cm⁻¹. EIMS m/z (%):218 (M⁺, 100), 203(10), 190(40), 153(12), 128(20). Anal. calc. For C₁₅H₁₀N₂: C, 82.55; H, 4.62; N, 12.84. Found C, 82.43; H, 4.68; N, 13.03.

2-[1-(4-Methoxy-phenyl)-ethylidene]-malononitrile (5d): (82%; from CHCl₃/Hexane, colourless crystals mp 76-77 °C). (Lit33. 76 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.62 (d, A part of AB system, J=9.0 Hz, 2H, ArH), 6.99 (d, B part of AB system, J=9.0 Hz, 2H, ArH), 3.87 (s, 3H, OCH₃), 2.61 (s, 3H, CH₃). ¹³C NMR (50 MHz, CDCl₃):175.88, 165.12, 131.79, 129.92, 116.48, 115.62, 115.36, 84.03, 57.58, 25.78. IR (KBr film): 3025, 2844, 2221, 1601, 1547, 1431, 1266, 1189, 1023, 842 cm⁻¹. EIMS m/z (%): 197 (M⁺, 100), 183(10), 155(18), 128(30).

2-(1-Biphenyl-4-yl-ethylidene)-malononitrile (5e): (70%; from CHCl₃/Hexane, light yellow crystals, mp 1064-165 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.76-7.63 (m, 5H, ArH), 7.61-7.41 (m, 4H ArH), 2.68 (s, 3H, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 176.62, 147.29, 141.31, 136.53, 131.08, 130.52, 130.10, 129.65, 129.19, 115.06, 114.92, 85.90, 26.10. IR (KBr film): 3050, 2225, 1630, 1562, 1465, 1373, 1288, 1176, 1014 cm⁻¹. EIMS m/z (%): 244 (M⁺, 100), 229(32), 189(10), 179(12), 152(20).

2-(1-Phanthen-3-yl-ethylidene)-malononitrile (5f): (78%; from CHCl₃/Hexane, yellow crystals mp 164-165 °C). ¹H NMR (200 MHz, CDCl₃): δ 8.97 (s, 1H, ArH), 8.69 (d, J=7.9 Hz, 1H, ArH), 7.97-7.67 (m, 7H, ArH), 2.79 (s, 3H, CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 177.19, 136.29, 135.47, 134.33, 132.10,132.04, 131.96, 131.47, 130.97, 129.60,129.62, 128.03, 126.58, 124.89, 124.57, 115.29, 115.01, 86.54, 26.37. IR (KBr film): 3056, 2952, 2228, 1566, 1428, 1285, 1239, 1181, 1150, 1035, 965 cm⁻¹. EIMS m/z (%): 268 (M⁺, 100), 253(54), 240(40), 202(20), 178(18), 120(14), 100(30). Anal. calc. For C₁₉H₁₂N₂: C, 85.05; H, 4.51; N, 10.44. Found C, 84.97; H, 4.63; N, 10.58.
The preparation of bromocrotononitriles 6a-f; typical procedure

To a stirred solution of crotononitriles 5a (1.1 g, 6.55 mmol) in 25 mL of CCl₄ was added dropwise a solution of bromine (0.53 g, 3.313 mmol) in 5 mL of CCl₄ at room temperature over 20 min. The reaction flask was irradiated with a 500-W sunlamp for 2 h (5e and 5f: 2 h; 5b: 6 h; 5c and 5d: 4 h). After evaporation of the solvent, the residue was filtered over silica gel (10 g) after eluting with hexane/chloroform (9:1). Removal of the solvent and recrystallisation from hexane/chloroform (4:1) gave 6a (1.41 g, 88%).

2-(2-Bromo-1-phenyl-ethylidene)-malononitrile (6a): (88%; colourless crystals, mp 111-112 °C, Lit.35. 113-116 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.65-7.50 (m, 5H, ArH), 4.56 (s, 2H, CH₂Br). ¹³C NMR (50 MHz, CDCl₃): δ 173.45, 134.90, 131.39, 130.95, 129.86, 113.56, 112.79, 88.65, 30.73. IR (KBr film): 3039, 2981, 2233, 1585, 1573, 1488, 1438, 1315, 1284, 1207, 1195, 1083, 998 cm⁻¹. EIMS m/z (%): 246/248 (M⁺, 14), 166/168(42), 140/142(100).

2-(2-Bromo-1-naphthalen-1-yl-ethylidene)-malononitrile (6b): (85%; from CHCl₃/Hexane, yellow crystals, mp 103-104 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.99-7.48 (m, 5H, ArH), 4.86 (s, 2H, CH₂Br). ¹³C NMR (50 MHz, CDCl₃): δ 174.73, 135.69, 134.02, 132.68, 131.26, 129.99, 129.09, 128.98, 128.88, 125.55, 113.18, 112.89, 93.25, 31.87. IR (KBr film): 3056, 2968, 2236, 1582, 1516, 1447, 1335, 1258, 1220, 1170, 1023, 912 cm⁻¹. EIMS m/z (%): 296/298 (M⁺, 24), 216/218(66), 188/190(100). Anal. calc. For C₁₅H₈BrN₂: C, 60.63; H, 3.05; N, 9.43. Found C, 60.54; H, 3.12; N, 9.37

2-(2-Bromo-1-naphthalen-2-yl-ethylidene)-malononitrile (6c): (82%; from CHCl₃, light yellow crystals, mp 152-153 °C). ¹H NMR (200 MHz, CDCl₃): δ 8.18 (m, 1H, ArH), 8.01-7.90 (m, 3H, ArH), 7.69-7.61 (m, 3H, ArH), 4.62 (s, 2H, CH₂Br). ¹³C NMR (50 MHz, CDCl₃): δ 172.61, 136.99, 134.52, 132.19, 131.48, 131.32, 131.23, 131.02, 129.96, 129.83, 125.39, 114.23, 113.54, 88.77, 30.57. IR (KBr film): 3031, 2981, 2233, 1627, 1585, 1500, 1438, 1365, 1211, 1168, 1126 cm⁻¹. EIMS m/z (%): 296/298 (M⁺, 60), 216/218(64), 188/190(100). Anal. calc. For C₁₅H₈BrN₂: C, 60.63; H, 3.05; N, 9.43. Found C, 60.81; H, 3.02; N, 9.30

2-[2-Bromo-1-(4-methoxy-phenyl)-ethylidene]-malononitrile (6d): (87%; from CHCl₃/Hexane, colourless crystals, mp 104-105 °C, Lit.36. 106-108 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.39 (d, A part of AB system J=9.0 Hz, 2H, ArH), 7.02 (d, B part of AB system J=9.0 Hz, 2H, ArH), 4.53 (s, 2H, CH₂Br), 3.88 (s, 3H, OCH₃). ¹³C NMR (50 MHz, CDCl₃): δ 172.16, 165.74, 132.41, 126.91, 116.90, 115.24, 114.35, 85.57, 57.45, 30.69. IR (KBr film): 3056, 2968, 2844, 2236, 1605, 1516, 1451, 1312, 1266, 1181, 1023, 958 cm⁻¹. EIMS m/z (%): 276/278 (M⁺, 64), 196/198(58), 180/182(100).

2-(1-Biphenyl-4-yl-2-bromo-ethylidene)-malononitrile (6e): (83%; from CHCl₃, light yellow crystals, mp 163-164 °C). ¹H NMR (200 MHz, CDCl₃): δ 7.75-7.62 (m, 5H, ArH), 7.53-7.43 (m, 4H, ArH), 4.60 (s, 2H, CH₂Br). ¹³C NMR (50 MHz, CDCl₃): δ 172.75, 145.98, 141.09, 133.56, 131.15, 130.73, 130.61, 129.93, 129.25, 114.75, 113.81, 88.05, 30.61. IR (KBr film): 3037, 2979, 2875, 2228, 1582s, 1485, 1447, 1324, 1216, 1189, 1079, 946 cm⁻¹. EIMS m/z (%): 322/324 (M⁺, 32), 242/244(68), 214/216(100). Anal. calc. For C₁₇H₁₁BrN₂: C, 63.18; H, 3.43; N, 8.67. Found C, 63.21; H, 3.55; N, 8.80

2-(2-Bromo-1-phenanthren-3-yl-ethylidene)-malononitrile (6f): (80%; from CHCl₃/Hexane, light red crystals, mp 164-165 °C). ¹H NMR (200 MHz, CDCl₃): δ 9.07 (d, J=1.8 Hz, 1H, ArH), 8.68 (d, J=7.8 Hz, 1H, ArH), 8.01 (d, J=8.4 Hz, 1H, ArH), 7.94 (d, J=7.4 Hz, 1H, ArH), 7.89 (d, J=8.9 Hz, 1H, ArH), 7.73-7.62 (m, 5H, ArH), 7.53-7.43 (m, 4H, ArH), 4.60 (s, 2H, CH₂Br). ¹³C NMR (50 MHz, CDCl₃): δ 172.75, 145.98, 141.09, 133.56, 131.15, 130.73, 130.61, 129.93, 129.25, 114.75, 113.81, 88.05, 30.61. IR (KBr film): 3037, 2979, 2875, 2228, 1582s, 1485, 1447, 1324, 1216, 1189, 1079, 946 cm⁻¹. EIMS m/z (%): 322/324 (M⁺, 32), 242/244(68), 214/216(100). Anal. calc. For C₁₇H₁₁BrN₂: C, 63.18; H, 3.43; N, 8.67. Found C, 63.21; H, 3.55; N, 8.80.
The preparation of aminothiophenes 9a-f; typical procedure

Bromocrotonitrile 6a (0.94 g, 3.84 mmol) was dissolved in a solution of dioxane (5 mL) and absolute ethanol (20 mL). The stirred solution was cooled to 0 °C, and then a suspension of NaSH (0.24 g, 4.29 mmol) in absolute ethanol (10 mL) was added dropwise over 30 min. The resulting reaction mixture was stirred for an additional 1 h at room temperature. After removal of the solvent, the residue was dissolved in hexane/ethylacetate (7:3) and the solution filtered over of 20 g neutral Al2O3 (activity-IV). After removing the solvent, the residue was crystallised from chloroform to yield 9a (655 mg, 85%).

2-Amino-4-phenyl-thiophene-3-carbonitrile (9a): (85%; colourless crystals, mp101-102°C, Lit 100-102°C). 1H NMR (200 MHz, CDCl3): δ 7.61-7.31 (m, 5H, ArH), 6.35 (s, 1H, H5), 5.24 (bs, 2H, NH2); 13C NMR (50 MHz, CDCl3): δ 165.65, 142.01, 136.23, 130.78, 130.22, 129.19, 117.83, 108.9, 90.63. IR (KBr film): 3421, 3309, 3101, 2210, 1631, 1504, 1442, 1396, 1195, 941 cm⁻¹. EIMS m/z (%): 200 (M⁺, 100), 172(18), 155(36), 128(10). Anal. calc. For C11H8NS: C, 65.97; H, 4.03; N, 13.99. Found C, 66.10; H, 4.33; N, 13.79.

2-Amino-4-naphthalen-1-yl-thiophene-3-carbonitrile (9b): (76%; from CHCl3, colourless crystals, mp 152-153°C). 1H NMR (200 MHz, CDCl3): δ 7.98-7.48 (m, 7H, ArH), 6.37 (s, 1H, H5), 4.92 (bs, 2H, NH2); 13C NMR (50 MHz, CDCl3): δ 164.43, 140.72, 135.79, 134.09, 133.73, 130.86, 130.39, 129.30, 128.43, 128.06, 127.43, 127.20, 117.14, 110.49, 93.47. IR (KBr film): 3415, 3300, 3092, 2215, 1638, 1515, 1415, 1384, 1207, 784 cm⁻¹. EIMS m/z (%): 250 (M⁺, 100), 233(10), 216(15), 207(24), 190(20), 163(14). Anal. calc. For C15H10N2S: C, 71.97; H, 4.03; N, 11.19. Found C, 65.60; H, 4.33; N, 13.79.

2-Amino-4-naphthalen-2-yl-thiophene-3-carbonitrile (9c): (74%; from CHCl3/Hexane, colourless crystals, mp 129-130°C). 1H NMR (200 MHz, CDCl3): δ 8.09 (s, 1H, ArH), 7.92-7.48 (m, 6H, ArH), 6.47 (s, 1H, H5), 4.94 (bs, 2H, NH2); 13C NMR (50 MHz, CDCl3): δ 165.55, 141.98, 135.98, 134.99, 133.52, 130.52, 130.31, 129.67, 128.49, 128.38, 128.09, 127.15, 117.83, 108.38, 90.84. IR (KBr film): 3428, 3326, 3122, 3054, 2204, 1640, 1610, 1514, 1402, 1198 cm⁻¹. EIMS m/z (%): 250 (M⁺, 100), 223(10), 216(15), 207(24), 190(20), 163(14). Anal. calc. For C15H10N2S: C, 71.97; H, 4.03; N, 11.19. Found C, 71.79; H, 4.30; N, 11.32.

2-Amino-4-(4-methoxy-phenyl)-thiophene-3-carbonitrile (9d): (81%; from CHCl3, white crystals, mp 154-155°C). 1H NMR (200 MHz, CDCl3): δ 7.52 (d, A part of AB system, J=8.9 Hz, 2H, ArH), 6.94 (d, B part of AB system, J=8.9 Hz, 2H, ArH), 6.23 (s, 1H, H5), 4.86 (bs, 2H, NH2). 13C NMR (50 MHz, CDCl3): δ 165.22, 121.68, 141.78, 130.31, 128.88, 117.83, 116.23, 106.82, 90.98, 57.33. IR (KBr film): 3449, 3326, 3210, 3114, 2201, 1624, 1508, 1393, 1254, 1157, 1023, 946 cm⁻¹. EIMS m/z (%): 230 (M⁺, 100), 215(42), 187(26), 143(10), 115(12).

2-Amino-4-biphenyl-4-yl-thiophene-3-carbonitrile (9e): (82%; from CHCl3, light yellow crys-
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tals, mp 192-193 °C). $^1$H NMR (200 MHz, DMSO-d$_6$): $\delta$ 7.78-7.64 (m, 5H, ArH), 7.54-7.39 (m, 4H, ArH), 7.32 (bs, 2H, NH$_2$), 6.63 (s, 1H, H$_5$). $^{13}$C NMR (50 MHz, DMSO-d$_6$): $\delta$ 168.29, 141.29, 139.69, 135.27, 130.76, 129.36, 129.15, 128.66, 128.34, 118.47, 106.93, 106.89, 84.89. IR (KBr film): 3372, 3314, 3210, 2209, 1651, 1509, 1408, 1293, 1200, 1123, 1081, 1004, 939 cm$^{-1}$. EIMS $m/z$ (%): 276 (M$^+$, 100), 248(10), 231(22), 216(10), 189(8), 152(8), 138(12), 110(20). Anal. calc. For C$_{17}$H$_{12}$N$_2$S: C, 73.88; H, 4.38; N, 10.14. Found C, 73.62; H, 4.40; N, 9.86.

2-Amino-4-phenanthren-3-yl-thiophene-3-carbonitrile (9f): (76%; from CHCl$_3$, brown crystals, mp 155-156 °C). $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.97 (bs, 1H, ArH), 8.74 (d, J=7.5 Hz, 1H, ArH), 7.96-7.76 (m, 2H, ArH), 7.74-7.58 (m, 5H, ArH), 6.55 (s, 1H, H$_5$), 4.92 (bs, 2H, NH$_2$). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 165.67, 142.21, 134.30, 134.12, 133.73, 132.44, 132.33, 131.05, 130.62, 129.49, 128.87, 128.41, 127.84, 127.52, 124.84, 123.26, 118.03, 108.37, 90.79. IR (KBr film): 3306, 3202, 3048, 2221, 1651, 1516, 1420, 1381, 1285, 1200, 1035, 958 cm$^{-1}$. EIMS $m/z$ (%): 300 (M$^+$, 100), 275(10), 260(16), 178(12), 125(15). Anal. calc. For C$_{19}$H$_{12}$N$_2$S: C, 75.97; H, 4.03; N, 9.33. Found C, 76.15; H, 4.06; N, 9.50.

Results and Discussion

In our methodology, we focused on the reaction of bromocrotonitriles 6a-f with NaSH for a facile synthesis of 2-aminothiophenes. For this purpose, we prepared crotonitriles 5a-f by the condensation of malononitrile with acetophenone derivatives by employing a known literature procedure.$^{32}$ Allylic bromination of crotonitriles was reported to result in low yields.$^{35,36}$ Crotonitriles may be efficiently brominated in allylic position by treatment with potassium tert-butoxide and then molecular Br$_2$.$^{38}$ Another allylic bromination procedure for crotonitriles was reported by refluxing in CCl$_4$.$^{39}$ In the present work, the reaction of crotonitriles 5a and 5d with NBS/AIBN at reflux temperature gave bromocrotonitriles 6a and 6d in moderate yields (56% and 39%). However, when the crotonitriles 5a-f were subjected to bromination under a project lamp (500 W mercury) at reflux temperature bromocrotonitriles 6a-f were obtained in high yields (80-88%). Bromocrotonitriles 6a-f were directly then converted into the desired 3,4-disubstituted-2-aminothiophenes 9a-f by anhydrous NaHS-promoted cyclisation. It is noteworthy that all the bromocrotonitriles 6a-f were completely cyclised to aminothiophene in high yields ranging from 74% to 85%.

Importantly, HS$^-$ reacts with 6a-f to afford unstable intermediates 7a-f, and then 8a-f, which are converted to 9a-f under the experimental conditions (Scheme 2).

In conclusion, the present work provides a facile synthesis of substituted-2-aminothiophenes via a stepwise Gewald reaction. In particular, the allylic bromination of acrilonitriles was improved. Thus, the methodology represents an improvement over the other methods in terms of total reaction yields.
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![Scheme 2]

Acknowledgements

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