Synthesis of a Spiro[cyclohex-1,1'-isobenzofuranyl] Dopamine Receptor Antagonist

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Abstract:

Two syntheses of the novel CNS agent, 2-fluoro-4-(*trans*)-(4-(3'H-spiro[cyclohex-1,1'-isobenzofuran]-4-yl)-piperazin-1-yl)benzonitrile, 1, are presented. The first relied on a reductive alkylation with low regioselectivity (1:1) but was sufficient for the preparation of kilogram quantities. The second used a selective ketone reduction of 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-4-one, 8, with sodium borohydride to provide the *cis*alcohol, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-(*cis*)-4-ol, 11. A simple process for the conversion of 11 to 1 is described. Regioselective reactions with 2,4-difluorobenzonitrile under mild conditions are described.

Recently, we conducted a kilogram-scale synthesis of 2-fluoro-4-(*trans*)-(4-(3'H-spiro[cyclohex-1,1'-isobenzofuran]-4-yl)-piperazin-1-yl)-benzonitrile **1**, a novel dopamine receptor antagonist discovered in the lab of Anton Fliri at Pfizer Central Research.² The synthesis originally used on lab scale by Fliri and co-workers had two key areas which were of concern for large-scale preparation. A protected piperazine starting material **4a** was used which was not available in large quantities, and the yield for the aromatic nucleophilic substitution reaction with **4a** indicated the possibility of a problem with the regiochemistry of the reaction with 2,4difluorobenzonitrile, **3**. More importantly, the diastereoselectivity of the reductive alkylation of the spiro-substituted cyclohexanone **8** with piperazine moiety **5b** gave a 3:2 ratio of isomers, favoring the undesired *cis*-isomer **2**.³

In the original process, the reaction of 2,4-difluorobenzonitrile **3** and N-BOC piperazine **4a** was carried out in dimethylsulfoxide solution at 140 °C in the presence of a slight excess of potassium carbonate for 24 h. The initial product **5a** was deprotected with HCl in ethanol to provide the hydrochloride salt of **5b** in <40% overall yield (Scheme 1). After it was found that the alkylation reaction with **4a** in dimethylformamide at 110 °C worked well, piperazine was tried due to the lack of a commercial source of **4a**. It was found that combining 2,4-difluorobenzonitrile **3** with piperazine in dimethylformamide or dimethylacetamide in the presence of potassium carbonate was mildly exothermic and the desired alkylation was proceeding at room temperature. Scheme 1



Further screening of solvents showed that **5b** could be formed directly by reaction of **3** with piperazine **4b** (2.6 equiv) and potassium carbonate (1 equiv) in acetonitrile at room temperature. The initial reaction mixture consisted of a 10:1 mixture of **5b** and its ortho isomer. Slurrying the crude solids in isopropyl ether gave pure **5b** in 71% yield. A similar selectivity for the displacement of the para-fluoride in **3** with alkoxides at low temperatures has been report by Wells and Shi.⁴

The preparation of spirocyclic ketone **8** was based on the work of Parham.⁵ 1,4-Cyclohexanedione mono-2,2-dimethyltrimethylene ketal **6** was treated with the dianion derived from 2-bromobenzyl alcohol and 2.2 equiv of *n*-butyllithium in tetrahydrofuran at - 60 °C to provide diol **7** in 79% yield.⁶ The next step of cyclization with loss of water and hydrolysis of the ketal was more complex than any of the earlier literature examples which involved formation of simpler spiro-isobenzofurans. A variety of acidic conditions have been described by Parham to produce either spiro-isobenzofurans or indenes related to **9** and **10** in our example

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⁽²⁾ Butler, T. W.; Fliri, A. F. J.; World Patent Application WO 9808835; Chem. Abs. 1998, 128, 2117296.

⁽³⁾ The isomers were named on the basis of the stereochemical relationship between the oxygen and nitrogen atoms attached to the cyclohexane ring. The *trans*-isomer 1 was desired.

⁽⁴⁾ Wells, K. M.; Shi, Y.-J.; Lynch, J. E.; Humphrey, G. R.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 6439–6442.

⁽⁵⁾ Parham, W. E.; Egberg, D. C. J. Org. Chem. **1972**, *37*, 1545–1549. Parham, W. E.; Montgomery, W. C. J. Org. Chem. **1974**, *39*, 2048–2050. Parham, W. E.; Sayed, Y. A. Synthesis **1976**, 116–117.

⁽⁶⁾ This monoketal 6 was available from Lancaster Synthesis Inc., Windham, NH 03087 in multikilogram quantities. Fliri used the mono-ethyleneketal of 1,4-cyclohexanedione which was available in research quantities only. This reaction could be run at 0 °C, but the lower temperature was used on scale-up to allow for shorter addition time. On lab scale, the use of 1 equiv of methyllithium to deprotonate the alcohol followed by *n*-butyllithium to form the dianion gave somewhat higher yields. Only *n*-butyllithium was used on scale-up to simplify the operations.



(Scheme 2). Two usable procedures were found. Fliri had surveyed numerous acidic conditions and found that treatment of 7 with 80% trifluoroacetic acid in water at room temperature effected the desired conversion. We extended the survey and discovered that 85% phosphoric acid at 50-60 °C worked well in the laboratory and that 8 could be precipitated by addition of water. The phosphoric acid procedure while preferable from a handling perspective was found to be more prone to give low levels of both 9 and 10 (up to 5 to 10%), and aqueous trifluoroacetic acid was used on a kilogram scale. Since the excess trifluoroacetic acid could not be evaporated from the reaction mixture on scaleup as was done in the lab, it needed to be neutralized. It was necessary to add a water-miscible organic solvent, tetrahydrofuran, before the neutralization of the trifluoroacetic acid with 25% sodium hydroxide solution to prevent the product from separating as an oil.

The final step in this approach to **1** was the reductive alkylation of piperazine **5b** with ketone **8** (Scheme 3). The original conditions were those of Abdel-Magid and Maryanoff using sodium triacetoxyborohydride as the reducing agent.⁷ This provided **1** and its diastereoisomer **2** with the nitrogen and the oxygen in a *cis* relationship in a 2:3 ratio. Surveying a large number of reductive alkylation conditions produced the following results. Hydrogenation over palladium on carbon in ethanol gave the same ratio of 2:3, while initial reaction with titanium tetraisopropoxide in ethanol followed by sodium borohydride gave 1:14 favoring the undesired isomer **2**.⁸ The use of the more hindered sodium tri-(2-ethylhexanoyloxy)-borohydride⁹ was one practical



Figure 1. Single-crystal X-ray structure of 12.¹¹

Scheme 4



method which at least improved the ratio of isomers to 1:1, and this was used on a large scale to produce 7.5 kg of 1. The yield for the final step at this scale was 34%, and compound 1 was isolated in high purity by crystallization from 2-propanol. Luckily, crystallization of mixtures of 1 and 2 from either ethanol or 2-propanol resulted in the removal of the undesired 2, even if it was the major component in the mixture.

While the reductive alkylation chemistry was used on a large scale, the low diastereoselectivity of the reaction caused us to examine other options. The reduction of ketone **8** with sodium borohydride in ethanol gave mainly one alcohol isomer **11** in 95% yield. The reaction of alcohol **11** with phthalimide under Mitsunobu conditions provided phthalimide **12** in 57% unoptimized yield¹⁰ (Scheme 4). The stereochemistry of **12** was proven by single-crystal X-ray analysis and was shown to have the desired relationship between the nitrogen substituent and the spiro-oxygen atom (Figure 1). The corresponding primary amine derived from **12** by hydrazinolysis of the phthalimide group was also formed in high yield, but introduction of a piperazine moiety was expected to require too many steps or hazardous alkylating reagents.

Displacement of the mesylate **13** which was available in high yield from alcohol **11** was considered next. Initial attempts to displace mesylate **13** with a stoichiometric amount of piperazine **5b** were unsuccessful in a variety of solvents, leading to either elimination of the mesylate or incorporation of the solvent in the case of alcohols. However, the reaction of **13** with an excess of piperazine **4b** (10:1 by weight) in a minimum of 2-propanol at reflux gave the desired piperazine derivative in 70% yield after an acid/base

⁽⁷⁾ Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. Tetrahedron Lett. 1990, 31, 5595–5598.

⁽⁸⁾ This was a variation on the work of Mattson who used sodium cyanoborohydride as the reducing agent. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. J. Org. Chem. 1990, 55, 2552–2554.

⁽⁹⁾ McGill, J. M.; LaBell, E. S.; Williams, M. A. Tetrahedron Lett. 1996, 37, 3977–3980.

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⁽¹¹⁾ The figure was plotted in Chem3D Plus (Cambridge Scientific Computing, Inc.) using the experimentally determined coordinates. Atomic coordinates have been deposited for the X-ray structure with the Cambridge Crystallographic Data Centre.



work up. The neutral fraction contained up to 15% of the olefin side product. The final coupling of piperazine 14 and difluorobenzonitrile 3 was done in refluxing acetonitrile in the presence of 1 equiv of potassium carbonate and provided 1 in 68% yield (Scheme 5).

In summary, two viable routes for scale-up have been demonstrated for the synthesis of a novel dopamine (D_4) antagonist. The preferred method utilized a diastereoselective sodium borohydride reduction and alkylation of piperazine with the secondary mesylate **13** to make a key bond connection. This synthesis also allowed for the introduction of the most expensive starting material **3** for this compound in the final synthetic step.

Experimental Section

The following procedures were from laboratory experiments and were followed as described in the large-scale preparation of 1 by the reductive alkylation process. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on either a Brucker WM 300 (300 MHz) or a Varian Unity 400 (400 MHz) spectrometer in deuteriochloroform. Infrared spectra were taken in KBr by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Mass spectra were determined with a Finnigan 4510 mass spectrometer using fast atom bombardment (FAB). Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY

9-(2-Hydroxymethyl-phenyl)-3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-ol (7). 2-Bromobenzyl alcohol (50 g, 0.267 mol) was dissolved in dry tetrahydrofuran (570 mL) and cooled to -60 °C under nitrogen. *n*-Butyllithium (246 mL of a 2.5 M solution in hexanes, 0.61 mol) was added dropwise over 20 min. The reaction was stirred at this temperature for 0.5 h. 1, 4-Cyclohexanedione mono-2, 2-dimethyl trimethylene ketal (74.1 g, 0.374 mole) in tetrahydrofuran (250 mL) was added dropwise over twenty min. The reaction was allowed to warm to -15 °C, and saturated aqueous ammonium chloride (750 mL) was added, and there was a mild exotherm which raised the final temperature to 15 °C. The reaction mixture contained some precipitated salts which were removed by filtration. The aqueous layer was separated, and the organics were washed with saturated ammonium chloride. The organic layer was concentrated in vacuo with addition of isopropyl ether to provide a slurry of solids in isopropyl ether with a volume of 250 mL. This was cooled to room temperature and diluted with hexanes (500 mL). The solids were collected, washed with hexanes, and dried in vacuo. The yield of white solids was 60.9 g, 74.4%: mp 128–132 °C. ¹HMR (CDCl₃, 400 MHz) δ 7.35–7.13 (m, 4), 4.81 (s, 2), 3.61 (s, 2), 3.54 (s, 2), 3.50 (s, 2), 2.40–1.70 (m, 8), 1.0 (s, 6).

3'H-Spiro[cyclohexane-1,1'-isobenzofuran]-4-one (8). Diol 7 (100 g, 0.326 mole) was dissolved in 80% trifluoroacetic acid and water (342 mL) at room temperature and was stirred overnight. The reaction was cooled to -20 °C, and tetrahydrofuran (210 mL) was added slowly with an exotherm noted. The reaction was recooled to 0 °C, and 25% sodium hydroxide solution ($\sim 200 \text{ mL}$) was added slowly to adjust the pH to 11.5. Water (700 mL) was added to the mixture to precipitate the product. The slurry was stirred overnight. The solids were filtered and reslurried in water (350 mL). The solids were collected and dried in vacuo. This material was suitable for use in the next step. The yield was 45.5 g, 69%: mp 102-106 °C. IR (KBr) 2221 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 2.16-2.11 (m, 4), 2.41-2.36 (m, 2), 2.95–2.83 (m, 2), 5.16 (s, 2), 7.11–7.08 (m, 1), 7.33-7.28 (M, 3). ¹³C NMR (CDCl₃) δ 37.0, 37.9, 71.1, 85.1, 120.5, 121.3, 127.5, 128.0, 138.8, 144.4, 211.6.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.21; H, 7.06.

HPLC: Inertsil, C-8, 5% acetonitrile/16% tetrahydrofuran/ 79% water, pH 3.2 with triethylamine phosphoric acid buffer; retention time: **8**, 16 min.

2-Fluoro-4-piperazin-1-yl-benzonitrile (5b). Piperazine (116 g, 1.35 mol) and potassium carbonate (74.5 g, 0.54 mol) were combined in acetonitrile (750 mL) under nitrogen. 2, 4-Difluorobenzonitrile 3 (75 g, 0.54 mol) in acetonitrile (188 mL) was added dropwise over 100 min with the reaction temperature starting at 15 °C and rising to 29 °C. The reaction was stirred at room temperature overnight. The inorganic solids were removed by filtration, and the filtrate was diluted with water (1125 mL). The mixture was concentrated under vacuum to remove most of the acetonitrile, and the aqueous layer was extracted with ethyl acetate (2.6 L). The organic layer was separated and washed with water $(3 \times 750 \text{ mL})$ and with brine (375 mL). The organics were dried over magnesium sulfate and concentrated in vacuo with the addition of isopropyl ether to achieve a final volume of 375 mL. The solids were collected, washed with fresh isopropyl ether, and dried in vacuo. The yield of solids was 79.5 g, 72%: mp 67–68 °C. ¹H NMR (CDCl₃, 400 MHz) δ 7.33 (dd, 1), 6.58 (dd, 1), 6.49 (dd, 1), 3.27–3.23 (m, 4), 2.97–2.93 (m, 4), 1.70 (s, 1). ¹³C NMR (CDCl₃) δ 166.5, 163.1, 155.7, 155.5, 133.81, 133.78, 115.4, 109.77, 109.75, 100.6, 100.3, 88.2, 87.8, 48.0, 45.6.

Anal. Calcd for C₁₁H₁₂FN₃: C, 64.37; H, 5.89, N, 20.47. Found: C, 64.33; H, 5.82; N, 20.35.

HPLC: Inertsil, C-8, 92.5% acetonitrile/7.5% pH 3.2 buffer (0.1% H_3PO_4 , 0.2% triethylamine): retention times: **5b**, 9.685 min; ortho-isomer, 14.2 min.

3'H-Spiro[cyclohexane-1,1'-isobenzofuran]-(*cis***)-4-ol (11).** Ketone **8** (3.21 g, 15.9 mmol) was dissolved in ethanol (32 mL) and cooled in an ice bath, while sodium borohydride (0.91 g, 23.8 mmol) was added as a solid. The ice bath was removed, and the reaction was stirred at room temperature overnight. The reaction solvent was evaporated in vacuo, and methylene chloride (30 mL) was added followed by 1 N HCl (30 mL). The layers were separated, and the organics were washed with brine, dried over magnesium sulfate, and evaporated to dryness. Isopropyl ether was added to the crude material. When crystallization began, the slurry was diluted with an equal volume of hexanes. The solids were collected and dried to provide 1.8 g of white solids, 56% yield: mp 117–118 °C. IR (KBr) 3456, 3422, 1477, 1460, 1443 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 7.27–7.18 (m, 3), 7.07 (m, 1), 5.05 (s, 2), 3.73 (m, 1), 1.96–1.67 (m, 9). ¹³C NMR (CDCl₃) δ 31.9, 35.3, 70.13, 70.4, 85.4, 120.5, 121.1, 127.2, 127.5, 138.9, 145.8. Mass spectrum (*m/e*) 204 (M⁺).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89 Found: C, 76.19; H, 7.87.

Methanesulfonic Acid 3'H-Spiro[cyclohex-1,1'-isobenzofuran]-(*cis*)-4-yl Ester (13). *cis*-Alcohol 11 was dissolved in methylene chloride (70 mL), and triethylamine (6.24 mL, 44.8 mmol) was added. The reaction was cooled in an ice bath, and methanesulfonyl chloride (3.55 mL, 44.8 mmol) was added dropwise. After 1 h, the reaction was washed with water and then with brine and was dried over magnesium sulfate. The solvent was evaporated in vacuo to provide the desired product as a white solid, 11.85 g, 98% yield: mp $123-124 \,^{\circ}$ C. IR (KBr) 3019, 2950, 2933, 1479, 1461, 1458, 1447, 1441 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 7.27–7.19 (m, 3), 7.05 (m, 1), 5.05 (s, 2), 4.78 (m, 1), 3.03 (s, 3), 2.11 (m, 4), 1.80 (m, 2), 1.76 (m, 2). ¹³C NMR (CDCl₃) δ 290, 35.1, 39.0, 70.9, 80.5, 84.6, 120.4, 121.2, 127.4, 127.8, 138.9, 144.9. Mass spectrum (*m/e*) 282 (M⁺).

Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55 H, 6.43 Found: C, 59.82; H, 6.23.

1-(3'H-Spiro[cvclohex-1,1'-isobenzofuran]-(trans)-4-vl)piperazine (14). Mesylate 13 (11.72 g, 41.6 mmol) and piperazine (117 g, 10 w/w) were combined in 2-propanol (120 mL) and heated to 114 °C for 28 h under nitrogen. The reaction was allowed to start cooling, and water (100 mL) was added while still warm. The mixture was diluted with more water (200 mL) and extracted with methylene chloride (3×100 mL). The methylene chloride was washed with water $(2 \times)$, and the solvent was replaced with ethyl acetate. The desired product was extracted from the ethyl acetate with 1 N sulfuric acid (2 \times 25 mL). The acidic aqueous layers were combined, and the pH was raised to pH 12 with 1 N NaOH. The basic aqueous layer was extracted with methylene chloride. The organics were washed with brine, dried over magnesium sulfate, and evaporated to a solid which was suitable for use in the next reaction. The yield was 7.85 g (70%): mp 118-119 °C. ¹H NMR (CDCl₃, 400 MHz) & 7.32–7.17 (m, 4), 5.03 (s, 3), 2.93 (m, 4), 2.53 (m, 4), 2.32 (m, 1), 2.04–1.82 (m, 7), 1.62 (m, 2). ¹³C NMR (CDCl₃) δ 24.6, 33.6, 46.6, 51.2, 60.1, 70.4, 86.9, 121.1, 121.5, 127.0, 127.3, 139.3, 146.3. Mass spectrum (m/e) 272 (M⁺).

2-Fluoro-4-(*trans***)-(4-(3'H-spiro**[cyclohex-1,1'-isobenzofuran]-4-yl)-piperazin-1-yl)-benzonitrile (1). (A) Sodium borohydride (18.7 g, 0.494 mole) was suspended in methylene chloride (750 mL) and treated with 2-ethylhexanoic acid (138 mL, 1.73 mol). This was stirred for 1 h, and the second half of the 2-ethylhexanoic acid (138 mL, 1.73 mol) was added. The mixture was stirred overnight at room temperature. A solution of 2-fluoro-4-piperazin-1-yl-benzonitrile 5b (40.6 g, 0.198 mol) and ketone 8 (50 g, 0.247 mol) in methylene chloride (300 mL) was added over five min, and the reaction was stirred for 7 h. Water (1000 mL) was added to the reaction mixture, which caused some gas evolution. The layers were separated, and the aqueous layer was extracted a second time with methylene chloride (250 mL). The combined organics were washed with water. The methylene chloride was removed by distillation at atmospheric pressure as isopropyl alcohol was added. The product crystallized from the 2-propanol and was collected. The yield was 26.16 g, 34%. This material contained <1% of the cisisomer 2. This was removed during the formation of the methanesulfonic acid salt.

HPLC: Inertsil, C-8, 5% acetonitrile/16% tetrahydrofuran/ 79% water, pH 3.2 with triethylamine phosphoric acid buffer: retention times: **1**, 11.4 min; **2**, 14.2 min.

(B) Substituted piperazine 14 (7.82 g, 28.8 mmol), 2,4difluorobenzonitrile 3 (4.4 g, 31.6 mmol), and potassium carbonate (4.36 g, 31.6 mmol were suspended in dry acetonitrile (80 mL) under nitrogen and heated to reflux for 24 h. The solution was cooled to room temperature and diluted with water (800 mL) to precipitate the crude product. The crude solids were refluxed in 95% ethanol (150 mL) overnight and then were stirred at room temperature for 1 h. The solid product was collected, washed with 2-propanol, and dried in vacuo to provide 7.47 g, 66% yield: mp 200-201 °C. IR (KBr) 2221 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 1.6 (m, 2), 1.9 (m, 4), 2.0 (m, 2), 2.4 (s, 1), 2.69 (m, 4), 3.37 (m, 4), 5.0 (s, 2), 6.63 (m, 2), 7.2 (m, 4), 7.4 (m, 1). ¹³C NMR (CDCl₃) δ 24.7, 33.0, 47.3, 49.4, 58.9, 70.5, 86.7, 100.4, 100.6, 109.7, 115.4, 121.1, 121.2, 127.1, 127.4, 133.9, 139.2, 146.2, 155.2, 155.3, 166.1. Anal. Calcd for C₂₄H₂₆-FN₃O: C, 73.63; H, 6.69; N, 10.73. Found: C, 73.30; H, 6.77; N, 10.69.

2-3'H-Spiro[cyclohex-1,1'-isobenzofuran]-(trans)-4-ylisoindole-1,3-dione (12). cis-Alcohol 11 (18.87 g, 92.5 mmol), triphenylphosphine (26.66 g, 101.8 mmol) and phthalimide (14.28 g, 97.1 mmol) were dissolved in tetrahydrofuran and stirred with ice-bath cooling, while diethyl azodicarboxylate (16 mL, 101.8 mmol) dissolved in tetrahydrofuran (25 mL) was added dropwise over 25 min. The reaction was warmed to room temperature and stirred overnight. The reaction was cooled in an ice-water bath. The solids were collected and washed with tetrahydrofuran. Concentration of the filtrate to lower volume gave a second crop. The combined crops were dried in vacuo to provide 17.8 g, 57% yield: mp 203-207 °C. ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (d, 1), 7.88 (m, 2), 7.75 (m, 2), 7.43–7.28 (m, 2), 7.20 (d, 1), 5.10 (s, 2), 4.40 (m, 1), 2.83 (dq, 2), 2.12-1.72 (m, 4). ¹³C NMR (CDCl₃) δ 25.6, 36.8, 49.4, 70.8, 86.2, 121.4, 123.3, 123.4, 127.5, 127.8, 132.3, 134.2, 139.9, 145.0, 168.8. The structure was confirmed by single-crystal X-ray analysis.

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.75; H, 5.79; N, 4.14.

Acknowledgment

We thank Dr. Jon Bordner of Pfizer Central Research for the determination of the single crystal X-ray structure of **12**.

Supporting Information Available

Experimental and crystallographic details. This material

is available free of charge via the Internet at http://pubs.acs.org.

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