New Routes to 3-(Arylthio)indoles: Application to the Synthesis of the 3,3′-Bis(indolyl) Sulfone Core of the Marine Alkaloid Echinosulfone A

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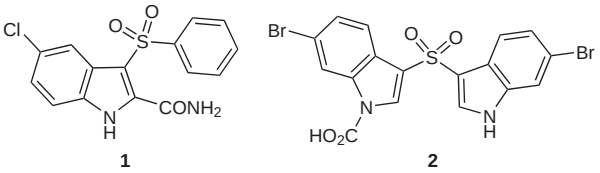
Received 15 May 2006

Abstract: A new approach to 3-(arylthio)indoles and related compounds has been developed, based on the reactions of aryl Grignard reagents or lithiated heteroaromatics with a phenylsulfonyl-protected 3,3′-bis(indolyl) disulfide. In addition, a rational approach to the 3,3′-bis(indolyl) sulfone core of the alkaloid echinosulfone A has been accomplished, involving treatment of a 3-lithioindole with bis(phenylsulfonyl) sulfide as the key step.

Key words: indoles, sulfides, sulfones, Grignard reagents, lithiation

Several synthetic routes to 3-(alkylthio)- or 3-(arylthio)indoles are available,[1] involving for example the use of disulfides,[1a] quinone-*O*,*S*-acetals,[1b] thiols in the presence of molecular oxygen,[1c] sulfenyl chlorides generated in situ,[1d] or *N*-thioalkyl- and *N*-thioarylphthalimides[1e] as the sulfenylating agents. Approaches utilizing sulfonyl chlorides[2a,b] or chlorosulfonic acid in acetonitrile[2c] have also been described. Although these procedures offer access to a variety of products, there are still many limitations, in particular concerning the accessibility and stability of the reagents. Both 3-(arylthio)indoles and the related sulfones have attracted considerable interest in medicinal chemistry. For instance, the sulfone L-737,126 (Figure 1, **1**) has been shown to exhibit potent anti-HIV properties,[3] triggering further efforts towards the design and biological evaluation of numerous related derivatives.[4] It was also demonstrated that several 3-(arylthio)indoles exhibited interesting activities as inhibitors of tubulin polymerization and growth of MCF-7 human breast cancer cells.[5] Despite all these studies, only a limited number of structures featuring a pair of indole units connected via a single sulfur atom bridge have been described.[6] A compound belonging to this class is the natural product echinosulfone A (Figure 1, **2**), which has been isolated from a southern Australian marine sponge, *Echinodictyum*.[7]

This background prompted us to initiate studies on the development of viable routes to the heterocyclic core of echinosulfone A (**2**). The only available approaches to 3,3′-bis(indolyl) sulfone or the corresponding sulfide are based on treatment of indole with alkylmagnesium halides, followed by introduction of sulfuryl chloride[6a] or sulfur.[6b] In our hands these methods gave only very low yields of pure products after laborious work-up and separation procedures, it was therefore desirable to develop alternative, practical approaches to such systems. To achieve this end, the readily available 3-bromo-1-(*tert*-butyldimethylsilyl)indole (**3**)[8] was subjected to halogen–metal exchange using *tert*-butyllithium, followed by treatment of the resulting 3-lithioindole derivative with 0.5 equivalents of bis(phenylsulfonyl) sulfide (Scheme 1).[9] This gave 3,3′-bis(indolyl) sulfide (**4**),[10] the structure of which was also supported by X-ray crystallography (Figure 2).[11] As anticipated, desilylation of **4** with TBAF in THF gave the parent sulfide **5**,[12] which was subsequently oxidized using Oxone® in aqueous acetone to give the target compound 3,3′-bis(indolyl) sulfone (**6**).[13] Interestingly, the sulfide **5** has previously been encountered as a side-product originating from the reaction of indolylmagnesium bromide with ethanesulfenyl chloride in connection with early synthetic studies towards 3-alkylthioindoles.[6c]



1 2

Figure 1

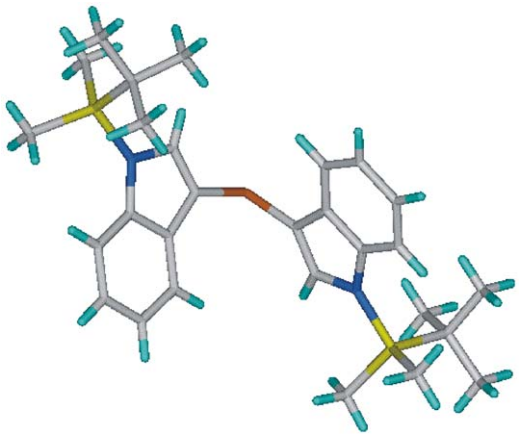
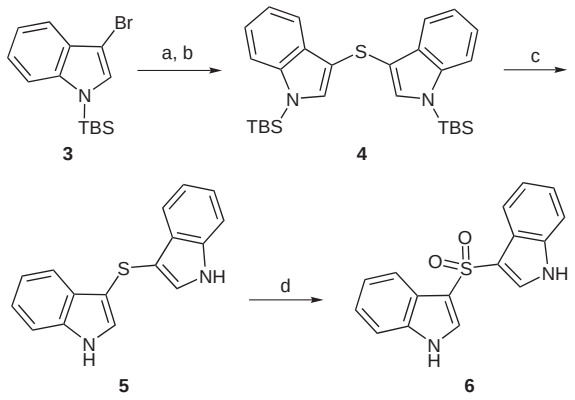


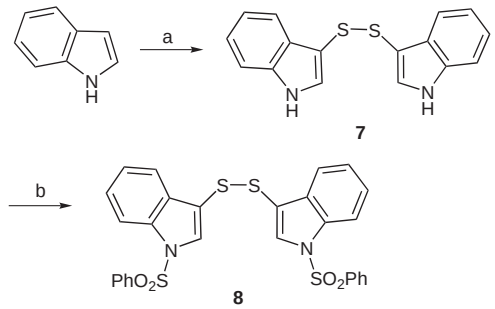
Figure 2 The crystal structure of the 3,3′-bis(indolyl) sulfide **4** determined at 200 K.

SYNLETT 2006, No. 15, pp 2459–2463
Advanced online publication: 08.09.2006
DOI: 10.1055/s-2006-950427; Art ID: G15206ST



Scheme 1 *Reagents and conditions*: (a) *t*-BuLi, THF, –78 °C, 0.5 h; (b) $(PhSO_2)_2S$, –78 °C to r.t., 16 h, 57%; (c) TBAF, THF, 0–5 °C, 1 h; then r.t., 20 min, 95%; (d) Oxone®, acetone, H_2O, r.t., 4 h, 70%.

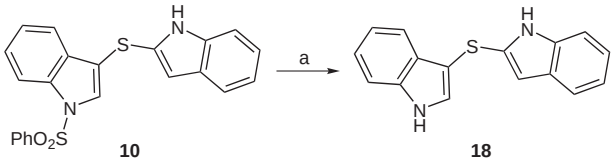
Cleavage of disulfides with organolithium or organomagnesium reagents is a well established approach to unsymmetrical sulfides. Hence, it was anticipated that treatment of suitably protected 3,3′-bis(indolyl) disulfides with C-metallated aromatics or heteroaromatics would constitute a route suitable for the preparation of a variety 3-(arylthio)- or 3-(heteroarylthio)indoles, as well as unsymmetrical 3,3′-bis(indolyl) sulfides. Consequently, the known disulfide **7** was prepared employing a modification of a literature procedure,[14] and the reported yield of 23% could be improved considerably to 60–80%, simply by passing a stream of air through the reaction mixture for several hours in order to facilitate the desired disulfide formation. The crude product may thereafter be conveniently purified by trituration with diisopropyl ether. We were pleased to note that the disulfide **7** proved to be remarkably stable under certain anhydrous basic conditions, as N-protection with benzenesulfonyl chloride using standard phase-transfer conditions[15] involving potassium hydroxide, produced compound **8**[16] in good yield, without cleavage of the disulfide linkage (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) H_2NCSNH_2, I_2, NaOH, EtOH, H_2O, air, r.t. 18–24 h, 60–80%; (b) $PhSO_2Cl$, *n*-Bu_4NHSO_4, KOH, CH_2Cl_2, 0 °C, 1 h, then r.t., 1.5 h, 72%.

With useful amounts of the disulfide **8** available, experiments involving lithiated heterocycles or aryl Grignard reagents were undertaken. Treatment of the 3-lithioindole (derived from **3**) with the disulfide **8**, gave the unsymmetrically protected 3,3′-bis(indolyl) sulfide **9** (Table 1) in moderate yield. Several other new 3-(heteroarylthio)- and 3-(arylthio)indoles (**10**–**17**) were prepared in a similar manner, and the results are summarized in Table 1.

In a further extension, it was demonstrated that the *N*-phenylsulfonyl group present in the resulting 3-thioindole products may be readily cleaved using aqueous potassium hydroxide in dioxane. This was illustrated by the conversion of 2,3′-bis(indolyl) sulfide (**10**) into the parent sulfide **18** (Scheme 3), which displayed spectral data fully consistent with the assigned structure.[22] This compound has been previously claimed as a product obtained by heating the indole with elemental sulfur at 115–125 °C for 48 hours.[23] However, comparison of our data with those given in the literature clearly disprove the previous assignment. In particular, a resonance (singlet) in the reported ^{1}H NMR data (DMSO-d_6) at $\delta = 4.77$[23] is not consistent with the spectrum obtained for **18**. Further detailed studies would be needed to provide full insight in this reaction. The formation of **18** during the heating of indole with sulfur is also contradicted by the fact that it is well established that this operation, when performed either in DMF or without solvent, gives predominantly a pentacyclic system, namely 5*H*,10*H*-[1,2,3,4]tetrathiocino[5,6-*b*:8,7-*b*′]diindole,[24] the structure of which has also been later corroborated by an independent synthesis, and finally supported by X-ray crystallography.[25]



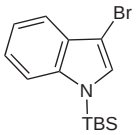
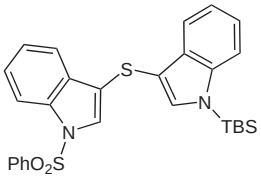
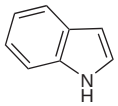
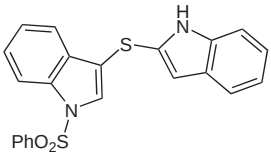
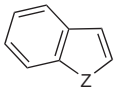
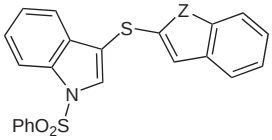
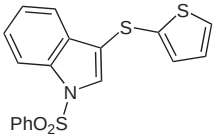
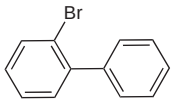
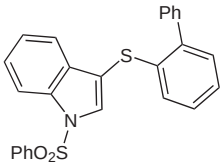
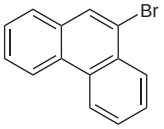
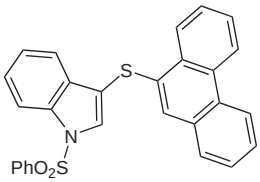
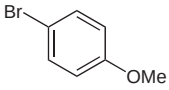
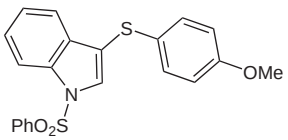
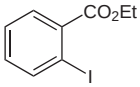
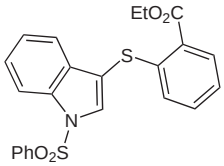
Scheme 3 *Reagents and conditions*: (a) 1 M KOH (aq)–dioxane (1:1), 80 °C, 15 min, 77%.

In conclusion, new and convenient synthetic routes to various 3-thioindoles incorporating both heterocyclic and carbocyclic moieties have been devised, involving reactions of lithiated heterocycles or aryl Grignard reagents with the 3,3′-bis(indolyl) disulfide **8**. These procedures offer efficient access to 3-thioindoles which are not practically available by the existing approaches. Further studies probing additional synthetic applications of the disulfide **8** and related compounds are in progress.

Acknowledgment

Mr. John Ogden, Varian Inc., is gratefully acknowledged for assistance with acquisition of the MS data.

Table 1 Reactions of Metallated Heterocycles and Aromatics with Disulfide **8**

Entry	Substrate	Reagents and conditions	Product	Yield (%)[a]
1	 **3**	(i) *t*-BuLi, THF, –78 °C[8] (ii) **8**, –78 °C to r.t., 16 h	 **9**	47
2		(i) BuLi, THF, –78 °C (ii) CO_2 (g) (iii) *t*-BuLi, THF, –78 °C[20] (iv) **8**, –78 °C to r.t.	 **10**	38
3	 Z = S, O	(i) BuLi, THF, –78 °C (ii) **8**, –78 °C to r.t.	 **11** Z = S **12** Z = O	76 (**11**)[17] 79 (**12**)
4		(i) BuLi, THF, –78 °C (ii) **8**, –78 °C to r.t.	 **13**	80
5		(i) Mg, I_2 (cat.), THF, reflux (ii) **8**, 0 °C to r.t.	 **14**	76[18]
6		(i) Mg, I_2 (cat.), THF, reflux (ii) **8**, 0 °C to r.t.	 **15**	62
7		(i) Mg, I_2 (cat.), THF, reflux (ii) **8**, 0 °C to r.t.	 **16**	77
8		(i) *i*-PrMgCl, THF, –20 °C to 0 °C[21] (ii) **8**, –78 °C to r.t.	 **17**	69[19]

[a] Yields of isolated products, based on disulfide **8**.

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(9) De Jong, F.; Janssen, M. J. *J. Org. Chem.* **1971**, *36*, 1645.

(10) Data for compound **4**: Colorless crystals, mp 160.5–161.5 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.81–7.75 (m, 2 H), 7.48–7.42 (m, 2 H), 7.39 (s, 2 H), 7.17–7.08 (m, 4 H), 0.91 (s, 18 H), 0.59 (s, 12 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 141.6, 134.9, 132.0, 122.0, 120.3, 119.7, 114.2, 109.1, 26.4, 19.6, –3.8; Anal. Calcd for $C_{28}H_{40}N_2SSi_2$: C, 68.23; H, 8.18; N, 5.68. Found: C, 68.25; H, 8.06; N, 5.59.

(11) Crystallographic data (excluding structure factors) for compound **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 606016. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].

(12) Data for compound **5**: Colorless crystals, mp 227.5–229 °C (Lit.[6b] 232 °C); IR (neat): 3409, 3393, 1452, 1405, 1335, 1236, 1085, 1002, 739 cm^{-1}; ^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 11.26 (s, 2 H), 7.74–7.70 (m, 2 H), 7.65 (d, *J* = 2.6 Hz, 2 H), 7.36–7.33 (m, 2 H), 7.10–7.00 (m, 2 H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 136.2, 129.7, 128.5, 121.5, 119.4, 118.6, 111.9, 105.3; ESI-MS: *m/z* = 263 $[M - H]^-$. The IR and ^{1}H NMR data are in good agreement with those discussed in reference 6c.

(13) Data for compound **6**: Colorless crystals, mp 304–306 °C; ^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 12.02 (s, 2 H), 8.22 (s, 2 H), 7.81–7.79 (m, 2 H), 7.44 (d, *J* = 7.4 Hz, 2 H), 7.21–7.11 (m, 4 H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 136.3, 130.1, 122.9, 122.8, 121.2, 118.7, 117.2, 112.6; ESI-MS: *m/z* = 295 $[M - H]^-$.

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(16) Preparation of disulfide **8**: A stirred suspension of finely powdered KOH (12.5 g, 0.22 mol) in CH_2Cl_2 (155 mL) under N_2 was cooled to 0 °C, followed by sequential addition of the disulfide **7** (14.8 g, 50 mmol), and tetrabutylammonium hydrogen sulfate (0.88 g, 2.6 mmol). To this mixture was added a solution of benzenesulfonyl chloride (16.0 mL, 0. 125 mol) in CH_2Cl_2 (25 mL) at 0 °C over 1.25 h. The resulting mixture was stirred at 0 °C for 1 h, and thereafter at r.t. for 1.5 h, whereupon it was filtered, and the filter cake was washed with several portions of CH_2Cl_2. Evaporation of the combined filtrates and washings gave a solid residue, which was recrystallized from MeCN (using activated carbon), to give **8** (20.9 g, 72%) as pinkish crystals, mp 165–166.5 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.02–7.98 (m, 2 H), 7.91–7.88 (m, 4 H), 7.62–7.48 (m, 10 H), 7.42–7.36 (m, 2 H), 7.27–7.22 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 137.8, 135.3, 134.5, 130.6, 130.4, 129.8, 127.1, 125.9, 124.1, 120.6, 115.8, 113.8; Anal. Calcd for $C_{28}H_{20}N_2O_4S_4$: C, 58.31; H, 3.50; N, 4.86. Found: C, 58.46; H, 3.58; N, 4.78.

(17) Compound **11** (Table 1, entry 3): To a solution of benzo[*b*]thiophene (0.24 g, 2.0 mmol) in anhydrous THF (10 mL) was added BuLi (2.5 M in hexanes, 0.80 mL, 2.0 mmol) over 10 min under N_2 at –78 °C. The solution was stirred for 30 min at –78 °C, followed by addition of a solution of the disulfide **8** (1.15 g, 2.0 mmol) in anhydrous THF (10 mL) over ~15 min at –78 °C. The mixture was allowed to warm to r.t. over 16 h, and was thereafter treated with sat. aq NH_4Cl (20 mL). The resulting mixture was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvents gave a residue, which was subjected to column chromatography on silica gel, initially using *n*-heptane followed by EtOAc–*n*-heptane (1:9 → 1:4), to provide **11** (0.64 g, 76%), as colorless crystals, mp 140–143 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.02–7.99 (m, 1 H), 7.93–7.90 (m, 2 H), 7.86 (s, 1 H), 7.65–7.56 (m, 4 H), 7.50–7.45 (m, 2 H), 7.39–7.23 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 141.4, 139.9, 138.0, 136.9, 135.4, 134.4, 130.8, 130.1, 129.6, 127.1, 126.4, 125.8, 124.7, 124.6, 124.2, 123.2, 122.0, 120.4, 114.0, 113.7; Anal. Calcd for $C_{22}H_{15}NO_2S_3$: C, 62.68; H, 3.59; N, 3.32. Found: C, 62.61; H, 3.68; N, 3.25.

(18) Compound **14** (Table 1, entry 5): A solution of 2-bromobiphenyl (0.56 g, 2.4 mmol) in anhydrous THF (5 mL) was added dropwise to a suspension of magnesium turnings (53 mg, 2.2 mmol) in anhydrous THF (5 mL) at r.t. under N_2. The mixture was heated at reflux for 1 h and was thereafter cooled to 0 °C, whereupon a solution of the disulfide **8** (1.15 g, 2.0 mmol) in anhydrous THF (10 mL) was added dropwise during ~15 min at 0 °C. The mixture was allowed to warm to r.t. over 16 h, followed by addition of 50% aq NH_4Cl (20 mL). Workup as for compound **11**, followed by column chromatography on silica gel, initially using *n*-heptane, followed by Et_2O–*n*-heptane (1:19 → 15:85), gave **14** (0.67 g, 76%) as colorless crystals, mp 128–130 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 1 H), 7.90–7.87 (m, 2 H), 7.69 (s, 1 H), 7.59–7.32 (m, 10 H), 7.26–7.15 (m, 3 H), 7.08–7.03 (m, 1 H), 6.84 (dd, *J* = 7.9, 0.9 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 141.0, 140.4, 138.0, 135.6, 135.0, 134.3, 131.3, 131.1, 130.5, 129.6, 129.5,

128.4, 128.1, 127.9, 127.5, 127.0, 125.9, 125.7, 124.1, 120.7, 114.0, 112.6; Anal. Calcd for $C_{26}H_{17}NO_2S_2$: C, 70.72; H, 4.34; N, 3.17. Found: C, 70.83; H, 4.39; N, 3.14.

(19) Compound **17** (Table 1, entry 8): A solution of *i*-PrMgCl (2.0 M in Et_2O, 1.2 mL, 2.4 mmol,) was added slowly (over ~10 min) to a solution of ethyl 2-iodobenzoate (0.55 g, 2.0 mmol) in anhydrous THF (10 mL) at –20 °C under N_2. The mixture was stirred at –20 °C for 30 min, and was then allowed to warm to 0 °C over 30 min. After cooling to –78 °C, a solution of the disulfide **8** (1.15 g, 2.0 mmol) in THF (10 mL) was added over ~15 min. The resulting mixture was allowed to warm to r.t. over 16 h, and was subsequently treated with sat. aq NH_4Cl (25 mL). Workup as for compound **11**, followed by column chromatography on silica gel using *n*-heptane–EtOAc (8:1), afforded **17** (0.60 g, 69%) as a colorless viscous oil, which solidified upon standing. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 8.08–8.02 (m, 2 H), 7.97–7.93 (m, 2 H), 7.90 (s, 1 H), 7.62–7.56 (m, 1 H), 7.51–7.46 (m, 2 H), 7.41–7.36 (m, 2 H), 7.25–7.19 (m, 1 H), 7.14–7.09 (m, 2 H), 6.69–6.66 (m, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.6, 141.6, 138.0, 135.8, 134.4, 132.5, 132.3, 131.4, 131.3, 129.6, 127.1, 126.8, 126.6, 125.8, 124.5, 124.2, 120.7, 114.0, 111.9, 61.5, 14.5.

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(22) Data for compound **18**: Off-white crystalline solid, mp 138–140 °C; ^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 11.55 (s, 1 H), 11.17 (s, 1 H), 7.75 (d, *J* = 2.5 Hz, 1 H), 7.59 (d, *J* = 7.7 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.7 Hz, 1 H), 7.23 (d, *J* = 8.1 Hz, 1 H), 7.16–7.11 (m, 1 H), 7.08–6.96 (m, 2 H), 6.93–6.88 (m, 1 H), 6.31 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ = 137.0, 136.3, 131.4, 131.1, 128.4, 128.0, 121.9, 121.0, 119.8, 119.1, 119.1, 118.4, 112.1, 110.8, 103.7, 100.8; ESI-MS: *m*/*z* = 265 $[M + H]^+$; Anal. Calcd for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.48; H, 4.65; N, 10.36.

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