Research Article

One-Pot Synthesis of Hypervalent Diaryl(iodo)bismuthanes from *o*-Carbonyl Iodoarenes by Zincation

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Diaryl(iodo)bismuthanes possessing a hypervalent C=O • • Bi-I bond were conveniently synthesized in a one-pot reaction by using arylzinc reagents generated from *o*-carbonyl iodobenzenes and zinc powder under ultrasonication. This method is superior to the conventional organolithium and Grignard methods because it has a wide functional group tolerance, requires no protecting group manipulations, and proceeds under mild reaction conditions that do not need low temperature control. Furthermore, no intermediate triarylbi-muthane precursor for the hypervalent iodobismuthane is necessary.

1. Introduction

Much effort has been devoted to the study of hypervalent bismuth(III) compounds [1–5]. Hypervalent bonds are formed efficiently via intramolecular coordination of a neutral donor to a bismuth(III) center [6–12]. We have used this method to synthesize various hypervalent organobismuth(III) compounds stabilized by intramolecular coordination and have characterized their molecular structures [13]. Furthermore, we have revealed that these compounds show antifungal activities against the yeast *Saccharomyces cerevisiae* [14, 15]. In particular, compounds **1** and **2**, which possess diary sulfone and acetophenone molecular scaffold, respectively, exhibited high antifungal activities.

These compounds are synthesized by directed *ortho*-lithiation (Scheme 1). Directed lithiation is a very useful and reliable synthetic method for introducing a molecular scaffold bearing an *ortho*-coordinative functional group, although the method can suffer from various practical difficulties. For example, the synthesis of **1** and **2** used triaryl-bismuthane as a precursor because the *ortho*-functionalized aryllithiums were too reactive to give **1** and **2** directly through

their reactions with BiI₃ and ArBiX₂, respectively. Furthermore, the acetyl substituent of acetophenone is incompatible with BuLi, meaning that the synthesis of **2** started from the protected silyl enol ether, and the harsh reaction conditions requiring excess BuLi caused the loss of Ar₂BiCl or the decomposition of the product, lowering the reproducibility of the yield [13, 14]. To facilitate the search for active antifungal compounds, a general and convenient synthetic method that has wide functional group compatibility for introducing various molecular scaffolds to the bismuth(III) center is required.

We have reported the synthesis under Grignard conditions of *p*-substituted triarylbi-muthanes **3** and **4**, which have a formyl and ester substituent, respectively (Scheme 2) [16]. The imino and ester substituents were tolerated despite their polarized double bond, although **3** required protection of the formyl substituent and **4** needed low-temperature control. Based on these results, we investigated using a type of organometallic reagent that is less reactive than Grignard reagents. Such an organometallic reagent would be compatible with carbonyl functional group and thus a suitable synthetic tool for use in our desired general method.

SCHEME 1: Synthesis of **1** and **2** by directed lithiation. SCHEME 2: Synthesis of **3** and **4**.

Several mild bismuth–carbon bond forming reactions have been reported, which include the treatment of aryl iodides with bismuth shot in the presence of Cu and CuI by ball milling [17], the arylation of bismuth(III) carboxylates by sodium tetraarylborate [18], and the reaction of BiCl₃ with organozinc reagents [19]. To achieve wide functional group tolerance, we chose organozinc reagents because they are compatible with carbonyl functionalities such as ester, acetyl, and even formyl substituents, and the chemistry of these reagents is well established [20–22]. Herein, we report the synthesis of hypervalent iodobismuthanes **2a** and **5a–10a**, which contain a carbonyl group, by zincation of the corresponding iodoarenes (Scheme 3). The organozinc method was superior to our previously reported organolithium and Grignard methods owing to the high functional group tolerance, short synthesis, mild reaction conditions, and acceptable yields.

2. Materials and Methods

All of the reactions were carried out under argon unless otherwise noted. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure. 1,4-Dioxane was distilled from calcium hydride. Diethyl ether was distilled from benzophenone ketyl before use. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ on a BRUKER AVANCE 400S spectrometer. Chemical shifts were referenced to residual solvent peak: chloroform

(7.26 ppm, 77.0 ppm) and DMSO (2.50 ppm, 40.45 ppm). IR spectra were obtained as KBr pellets on a Nicolet FT-IR Impact 410 spectrophotometer. Melting points were determined on a YANAGIMOTO melting point apparatus without correction. Elemental analysis was performed on a MICRO CORDER JM10 apparatus (J-SCIENCE LAB. Co.). HRMS were recorded on a Bruker Daltonics micrOTOF II (APCI) instrument. 2'-Iodoacetophenone and ethyl 2-iodobenzoate were commercially available. 2-Iodobenzaldehyde, 4-fluoro-2-iodobenzaldehyde, 2-iodo-5-methoxybenzaldehyde, 4'-fluoro-2'-iodoacetophenone, and 3-iodothiophene-2-carboxaldehyde were prepared in high yields by Finkelstein reaction of the corresponding bromoarenes in accordance with the literature [23].

2.1. Typical Procedure for the Finkelstein Reaction of Bromoarenes. To a round-bottomed flask (50 mL) equipped with a magnetic stir bar were added bromoarene (2.5 mmol), CuI (5 mol%), NaI (5 mmol), and 1,3-diaminopropane (10 mol%). After dry 1,4-dioxane (2.5 mL) was added to the flask, the mixture was refluxed for 24 h. The reaction was quenched with water (30 mL) at room temperature and the resulting mixture was extracted with ethyl acetate (3 × 30 mL). The organic layer was dried (Na₂SO₄) and concentrated to leave a residue, which was chromatographed on silica gel with hexane–ethyl acetate (5:1) to give the corresponding iodoarene, which was used in the next step without further purification.

SCHEME 3: Hypervalent iodobismuthanes functionalized with a carbonyl group.

2.2. 2-Iodobenzaldehyde. Yield 99% (574 mg, 2.48 mmol), Colorless solid, mp 39–41°C. ^1H NMR (400 MHz, CDCl_3): δ 7.29 (1H, dt, $J = 7.6$ Hz, 1.6 Hz), 7.47 (1H, t, $J = 7.6$ Hz), 7.89 (1H, dd, $J = 7.6$ Hz, 1.6 Hz), 7.96 (1H, d, $J = 8.0$ Hz), 10.08 (1H, s).

2.3. 4-Fluoro-2-Iodobenzaldehyde. Yield 97% (606 mg, 2.43 mmol), Colorless solid, mp 49–51°C. ^1H NMR (400 MHz, CDCl_3): δ 7.19 (1H, m), 7.68 (1H, m), 7.91 (1H, m), 9.99 (1H, d, $J = 2.4$ Hz).

2.4. 2-Iodo-5-Methoxybenzaldehyde. Yield 98% (642 mg, 2.45 mmol), Colorless solid, mp 113–116°C. ^1H NMR (400 MHz, CDCl_3): δ 3.84 (3H, s), 6.92 (1H, dd, $J = 8.4$ Hz, 3.2 Hz), 7.43 (1H, d, $J = 3.2$ Hz), 7.80 (1H, d, $J = 8.4$ Hz), 10.02 (1H, s).

2.5. 4'-Fluoro-2'-Iodoacetophenone. Yield 98% (647 mg, 2.45 mmol), Colorless solid, mp 45–46°C. ^1H NMR (400 MHz, CDCl_3): δ 2.59 (3H, s), 7.11 (1H, m), 7.52 (1H, m), 7.65 (1H, m).

2.6. 3-Iodothiophene-2-Carboxaldehyde. Yield 99% (589 mg, 2.48 mmol), Colorless solid, mp 82–85°C. ^1H NMR (400 MHz, CDCl_3): δ 7.28 (1H, d, $J = 4.8$ Hz), 7.70 (1H, dd, $J = 4.8$ Hz, 1.2 Hz), 9.83 (1H, d, $J = 1.2$ Hz).

2.7. Typical Procedure for the Synthesis of Aryl(iodo)(4-methylphenyl)bismuthane. To a round-bottomed flask (50 mL) equipped with a magnetic stir bar were added bismuth(III) chloride (422 mg, 1.33 mmol) and tris(4-methylphenyl)bismuthane (323 mg, 0.67 mmol). After dry diethyl ether (6 mL) was added to the flask at room temperature, the mixture was stirred for 1 h. To another round-bottomed flask (50 mL) were added iodoarene (1 mmol), zinc powder (262 mg, 4 mmol), and dry DMF (5 mL). The flask was set in an ultrasonic water bath at room temperature (25°C) and the resulting mixture was sonicated for 1.5–4 h, during which time the water bath temperature rose to 48°C. The sonication was stopped and unreacted zinc powder precipitated. The resulting supernatant solution containing an arylzinc reagent was slowly transferred to the suspension of dichloro(4-methylphenyl)bismuthane (ca. 2 mmol) thus formed, and the resulting mixture was stirred for 3.5–8 h at room temperature. The reaction was quenched with a saturated aqueous solution of NaI (3 mL) and the resulting mixture was extracted with ethyl acetate (3 $\times$ 50

mL). The combined extracts were concentrated to leave an oily residue, which was chromatographed on silica gel with hexane–ethyl acetate (5:1) to afford the corresponding iodobismuthane.

2.8. (2-Acetylphenyl)iodo(4-methylphenyl)bismuthane 2a. Yellow crystal, Yield 35% (191 mg, 0.35 mmol), mp 160–162°C. ^1H NMR (400 MHz, CDCl_3): δ 2.25 (3H, s), 2.69 (3H, s), 7.25 (2H, d, $J = 8.0$ Hz), 7.71 (1H, dt, $J = 7.6$ Hz, 1.2 Hz), 7.88 (1H, dt, $J = 7.6$ Hz, 1.2 Hz), 8.07 (2H, d, $J = 8.0$ Hz), 8.22 (1H, dd, $J = 7.6$ Hz, 1.2 Hz), 9.41 (1H, dd, $J = 7.2$ Hz, 0.8 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 21.54, 27.08, 128.50, 132.36, 134.51, 138.01, 138.21, 138.98, 143.10, 145.55, 166.78, 172.09, 207.54. IR (KBr): ν 3738, 3037, 1622, 1552, 1276 and 761 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{13}\text{BiO}$: $[\text{M}-\text{H}]^-$ 544.9832. found: 544.9821.

2.9. (2-Acetyl-5-fluorophenyl)iodo(4-methylphenyl)bismuthane 5a. Yellow crystal, Yield 28% (158 mg, 0.28 mmol), mp 186–188°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.19 (3H, s), 2.72 (3H, s), 7.29 (2H, d, $J = 7.6$ Hz), 7.54 (1H, dt, $J = 8.4$ Hz, 2.0 Hz), 8.11 (2H, d, $J = 7.6$ Hz), 8.55 (1H, dd, $J = 8.4$ Hz, 4.8 Hz), 8.89 (1H, br-s). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 21.13, 27.48, 115.62 (d, $J = 22.6$ Hz), 130.94 (br-d), 132.08($\times 2$), 137.09, 138.45, 138.85 (d, $J = 8.0$ Hz), 140.51, 169.52, 172.12, 207.85. IR (KBr): ν 1620, 1575, 1558, 1358, 1299, 1262 and 1201 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{12}\text{BiFO}$: $[\text{M}-\text{H}]^-$ 562.9730. found: 562.9726.

2.10. (2-Formylphenyl)iodo(4-methylphenyl)bismuthane 6a. Yellow crystal, Yield 56% (298 mg, 0.56 mmol), mp 143–144°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.21 (3H, s), 7.30 (2H, d, $J = 7.6$ Hz), 7.86 (1H, t, $J = 7.2$ Hz), 7.95 (1H, t, $J = 7.2$ Hz), 8.14 (2H, d, $J = 7.6$ Hz), 8.44 (1H, d, $J = 7.2$ Hz), 9.02 (1H, d, $J = 7.2$ Hz), 10.75 (1H, s). ^{13}C NMR (100 MHz, CDCl_3): δ 21.55, 128.65, 132.47, 137.58, 138.23, 138.44, 139.63, 143.66, 146.16, 165.99, 170.92, 199.50. IR (KBr): ν 3058, 2857, 1633, 1572, 1553, 1296 and 1207 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{14}\text{H}_{13}\text{BiO}$: $[\text{M}+\text{H}]^+$ 532.9808. found: 532.9810.

2.11. (2-Formyl-5-fluorophenyl)iodo(4-methylphenyl)bismuthane 7a. Yellow crystal, Yield 29% (195 mg, 0.29 mmol), mp 148–149°C. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.21 (3H, s), 7.32 (2H, d, $J = 7.6$ Hz), 7.61 (1H, dt, $J = 8.4$ Hz, 2.4 Hz), 8.18 (2H, d, $J = 7.6$ Hz), 8.52 (1H, dd, $J = 8.0$ Hz, 5.2 Hz), 8.74 (1H, d, $J = 6.4$ Hz), 10.74 (1H, s). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$):

SCHEME 4: Conventional synthesis of **6** by directed lithiation.

δ 21.14, 115.75 (d, $J = 22.7$ Hz), 131.83 (br-s), 132.17($\times 2$), 137.05, 139.01, 140.73 (d, $J = 9.0$ Hz), 140.88, 169.19, 171.80, 199.67. IR (KBr): ν 3061, 2875, 1638, 1582, 1561, 1259 and 1204 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{14}\text{H}_{10}\text{BiFIO}$: $[\text{M}-\text{H}]^-$ 548.9566. found: 548.9570.

2.12. (2-Formyl-4-methoxyphenyl)iido(4-methylphenyl)bismuthane **8a**. Yellow crystal, Yield 31% (175 mg, 0.31 mmol); mp 146–147°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.22 (3H, s), 3.87 (3H, s), 7.31 (2H, d, $J = 8.0$ Hz), 7.48 (1H, dd, $J = 7.6$ Hz, 2.8 Hz), 7.99 (1H, d, $J = 2.8$ Hz), 8.13 (2H, d, $J = 7.6$ Hz), 8.78 (1H, d, $J = 8.0$ Hz), 10.66 (1H, s). ^{13}C NMR (100 MHz, CDCl_3): δ 21.57, 55.67, 122.95, 125.69, 132.38, 138.20, 138.31, 145.09, 147.94, 160.26, 161.34, 166.38, 199.13. IR (KBr): ν 3027, 2924, 2862, 1640, 1585, 1552, 1460, 1251 and 1044 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{15}\text{H}_{13}\text{BiIO}_2$: $[\text{M}-\text{H}]^-$ 560.9770. found: 560.9770.

2.13. (2-Formyl-3-thienyl)iido(4-methylphenyl)bismuthane **9a**. Yellow crystal, Yield 53% (287 mg, 0.53 mmol), mp 132–133°C. ^1H NMR (400 MHz, CDCl_3): δ 2.28 (3H, s), 7.31 (2H, d, $J = 7.6$ Hz), 8.04 (1H, d, $J = 4.4$ Hz), 8.09 (1H, d, $J = 4.4$ Hz), 8.14 (2H, d, $J = 7.6$ Hz), 10.12 (1H, s). ^{13}C NMR (100 MHz, CDCl_3): δ 21.58, 132.67, 138.50, 138.56, 142.08, 145.66, 148.47, 166.97, 174.32, 186.44. IR (KBr): ν 1586, 1483, 1450, 1397, 1337, 1195, 853 and 794 cm^{-1} . HRMS (APCI) calcd. for $\text{C}_{12}\text{H}_{11}\text{BiIOS}$: $[\text{M}+\text{H}]^+$ 538.9374. found: 538.9374.

2.14. (2-Ethoxycarbonylphenyl)iido(4-methylphenyl)bismuthane **10a**. Yellow crystal, Yield 61% (351 mg, 0.61 mmol), mp 125–126°C. ^1H NMR (400 MHz, CDCl_3): δ 1.40 (3H, t, $J = 7.2$ Hz), 2.26 (3H, s), 4.43 (2H, m), 7.26 (2H, d, $J = 7.6$ Hz), 7.36 (1H, dt, $J = 7.6$ Hz, 0.8 Hz), 7.84 (1H, dt, $J = 7.6$ Hz, 1.2 Hz), 8.09 (2H, d, $J = 7.6$ Hz), 8.22 (1H, dd, $J = 7.6$ Hz, 1.2 Hz), 9.43 (1H, d, $J = 7.2$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 14.09, 21.54, 63.31, 128.29, 132.28, 132.77, 134.35, 137.96, 138.27, 138.70, 143.83, 166.84, 169.52, 175.85. IR (KBr): ν 2990, 1634, 1573, 1373, 1311, 1005, 785 and 733 cm^{-1} . Anal. Calc. for $\text{C}_{16}\text{H}_{16}\text{BiIO}_2$: C, 33.35; H, 2.80. Found: C, 33.32; H, 3.03.

3. Results and Discussion

Initially, we tried the one-pot synthesis of **10a** by the zincation of ethyl 2-iodobenzoate. The arylzinc was prepared by using the method reported by Takagi and coworkers [20], who treated iodoarenes containing an electron-withdrawing substituent, such as a methoxycarbonyl or an acetyl substituent,

at the ortho position in the presence of zinc powder under ultrasonication at 30°C.

When a mixture obtained by sonicating ethyl 2-iodobenzoate with zinc powder (1 equiv) at 25°C in DMF was allowed to react with TolBiCl_2 (1 equiv), **10a** was obtained in only 4% yield (Table 1, Entry 1). The poor yield was attributed to the incomplete conversion of the starting iodoarene to the arylzinc. The yield of **10a** was increased by increasing the equivalents of zinc powder and TolBiCl_2 (Entries 2 and 3). Furthermore, an increase in the temperature from 25 to 48°C during the sonication accelerated the zincation reaction (Entries 4–9). The reaction mixture turned dark yellow during the zincation, which was a good indicator for the completion of the reaction. The yield of **10a** was sensitive to the zinc powder loading and the best result was obtained when 4 equiv zinc powder and 2 equiv TolBiCl_2 were used (Entry 7). Higher zinc powder or TolBiCl_2 loadings decreased the yield of **10a** (Entries 8 and 9).

Encouraged by the success of the one-pot synthesis of **10a**, we performed the one-pot syntheses of **2a** and **5a**, which have an acetophenone scaffold, using the reaction conditions used in the synthesis of **10a** (Table 1, Entry 7). After the zincation reaction mixtures had turned dark yellow, the arylzinc was allowed to react with TolBiCl_2 , followed by quenching with a saturated aqueous solution of NaI to give **2a** and **5a** in 35% and 28% yields, respectively, despite the presence of acidic acetyl protons (Table 2, Entries 1 and 2). We have previously reported that the synthesis of **5a** from the corresponding silyl enol ether by conventional directed lithiation failed (Scheme 1) [14]. We explained the failure by the presence of the fluoro substituent, which can act as a directing group. The success in obtaining **5a** demonstrates the usefulness of the zincation method.

Furthermore, we used this method to synthesize **6a–9a**, which have a formyl substituent (Entries 3–6). We have previously reported the synthesis of **6** by the directed *ortho*-lithiation of lithium α -amino alkoxide (Scheme 4) [13]. This method required excess BuLi, which often caused the loss of Ar_2BiCl or decomposition of the product by overreaction with unreacted BuLi. In addition, the lithium alkoxide moiety could form an undesired bismuth alkoxide by reacting with Ar_2BiCl . Hence, the present zincation overcomes these drawbacks. In particular, **7a**, **8a**, and **9a** were obtained in acceptable yields by the zincation; if conventional directed lithiation was used, the fluoro and methoxy substituents in **7a** and **8a**, respectively, would act as directing groups and the thienyl ring proton α to the sulfur atom in **9a** would undergo undesired lithiation.

TABLE 1: Optimization of the reaction conditions for the synthesis of **10a**.

Entry	Zn (equiv)	TolBiCl ₂ (equiv)	Ultrasound Temp (°C)	Ultrasound Time (h)	Yield (%) 10a
1	1.0	1.0	25	6	4
2	1.5	1.0	25	6	9
3	2.0	1.5	25	5	14
4	2.5	1.5	25–48	3	18
5	3.0	2.0	25–48	4	28
6	3.5	2.0	25–48	4	41
7	4.0	2.0	25–48	4	61
8	4.5	2.0	25–48	5	60
9	4.0	3.0	25–48	5	55

TABLE 2: Synthesis of iodobismuthanes.

Entry	ArI	Ultrasound Time (h)	TolBiCl ₂ Time (h)	ArBi(Tol)I	Yield (%)
1		2.0	3.5	2a	35
2		1.5	6.0	5a	28
3		3.5	8.0	6a	56
4		3.0	8.0	7a	29
5		3.5	8.0	8a	31
6		4.0	8.0	9a	53

The molecular structure of **2** (Ar = Tol, X = Br) has been characterized by X-ray structure analysis and ^{13}C NMR and IR spectra, which reveals the formation of a hypervalent O–Bi–Br bond by the intramolecular coordination of the carbonyl group with the bismuth atom [13]. The hypervalent bond formation was also detected in the ^1H NMR spectra. The ^1H NMR spectrum of **2a** in CDCl_3 shows anisotropic deshielding (δ 9.41 ppm) of the *ortho* proton adjacent to the bismuth atom in the arylcarbonyl scaffold because of its close proximity to the electronegative iodine atom owing to the hypervalent O–Bi–I bond formation [14]. Compound **10a** showed a similar deshielding of the *ortho* proton signal at δ 9.43 ppm in CDCl_3 , which is consistent with hypervalent bond formation. In contrast, no large deshielding of the aromatic proton was observed in the thienyl ring proton of **9a**. This may be attributed to the signal for the α -proton of the thienyl ring being shifted downfield because of the effect of the sulfur atom. As a result, the signal due to the β -proton is apparently not affected by anisotropic deshielding by the iodine atom.

4. Conclusions

Hypervalent iodobismuthanes bearing a carbonyl group were synthesized easily with a one-pot reaction using arylzinc reagents. The zinc reagents tolerated carbonyl group, acetyl protons, and ring protons adjacent to fluoro, methoxy, and sulfur functional groups. This indicates that the zincation reaction may be suitable for synthesizing a wide range of hypervalent antifungal bismuth(III) compounds with various molecular scaffolds.

Data Availability

The ^1H and ^{13}C NMR spectral data used to support the findings of this study are included within the supplementary information file.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

See Figures S1–S5 [the ^1H NMR spectra of *o*-carbonyl iodoarenes] and Figures S6–S19 [the ^1H and ^{13}C NMR spectra of compounds **2a** and **5a–10a**]. (Supplementary Materials)

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