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A novel dry route to *ortho*-functionalized triarylbismuthanes that are difficult to access by conventional wet routes

Mika Urano, Shinobu Wada and Hitomi Suzuki*
Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, Gakuen 2-1, Sanda 669-1337, Japan. E-mail: hsuzuki@ksc.kwansei.ac.jp; Fax: +81-79-565-9077

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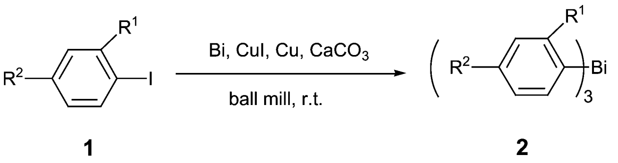
When an aryl iodide bearing an electron-withdrawing group at the *ortho* position was milled together with bismuth shots and calcite grains in the presence of Cu powder and CuI using a laboratory ball mill, the corresponding *ortho*-functionalized triarylbismuthane was obtained in moderate to good yield.

Triarylbismuthanes are usually prepared *via* the organometallic route, which involves the reaction of aryl Grignard or aryllithium reagent with anhydrous bismuth(III) halides.[1] This methodology has wide applicability as far as arylmagnesium and aryllithium reagents are available. When functionalized triarylbismuthanes are needed, however, they are subject to some limitations, since many functional groups are incompatible with these organometallic compounds due to their readiness to react.

In recent years, an important breakthrough has been made by Knochel and co-workers[2] where the aromatic Grignard reagent bearing a sensitive functional group such as carbonyl, cyano, nitro, or ester group can be obtained by the halogen–magnesium exchange between a substituted aryl iodide and isopropylmagnesium bromide at low temperature. The halogen–lithium exchange between activated aryl halides and phenyllithium has also been known for a long time[3] and used for the preparation of some functionalized triarylbismuthanes.[4] In our experience, however, the preparation of these functionalized organometallic reagents requires some skill and, when applied to the synthesis of functionalized triarylbismuthanes, the results are often disappointing. Direct treatment of functionalized organometallic reagents with $BiCl_3$ lead in most cases to an intractable tarry substance. Thus, we wish to report herein a new alternative to the synthesis of *ortho*-functionalized triarylbismuthanes, where the whole process can be carried out in a single pot in the absence of any organic solvent. Though limited in scope at present, it provides a short convenient route† to some *ortho*-functionalized triarylbismuthanes that are laborious or difficult to obtain by conventional wet methods.

Aryl halides are inert toward bismuth metal on either simple mixing or heating at elevated temperatures. However, when an aryl iodide **1** bearing an electron-withdrawing substituent at the *ortho* position was milled together with bismuth shots and calcite grains in the presence of Cu powder and CuI using a laboratory ball mill at room temperature, there resulted the corresponding *ortho*-functionalized triarylbismuthane **2** in moderate to good yield (Scheme 1). It was observed that the nature and relative position of substituent groups on the aromatic ring strongly influence the yield of the products. The electron-withdrawing group at the *ortho*-position favored the formation of triarylbismuthane, while those at the *meta* and *para* positions as well as the electron-donating group worked negatively, leading to little or no formation of the expected product.



Scheme 1

The importance of the relative location of the substituent groups on the aromatic ring was well manifested in the reaction of iodonitrobenzenes. The *ortho* isomer **1j** gave the expected triarylbismuthane **2j**, while the *para*-isomer underwent reductive coupling to produce 4,4′-diiodoazoxybenzene[5] and the *meta*-isomer gave a complex mixture of reduction and coupling products. These results are in accordance with an early report that *o*-lithiated nitrobenzene was obtained by the halogen–lithium exchange between 1-bromo-2-nitrobenzene and phenyllithium at −100 °C, but similar attempts to obtain the *m*- or *p*-lithiated nitrobenzene failed.[3] Attempted halogen–metal exchange between *o*-fluoroiodobenzene and isopropylmagnesium bromide or butyllithium led to a complex mixture of unidentified products, which may be attributed to the high nucleofugal nature in solution of the fluorine atom adjacent to the anionic carbon center.[6] In this regard, good results obtained from **1b–d** were noteworthy (Table 1). When the aryl iodides contained a proton source such as carboxyl and hydroxyl groups, no reaction took place. Interestingly, the presence of cyano and pyridyl groups also inhibited the reaction. These observations may be taken to suggest a possible inactivation of a reactive metal intermediate by the ligating substituent group, which would coordinate to the metal center *via* a nitrogen or oxygen atom.

A combination of Bi and Cu or CuI is indespensable for the present reaction, and the combined use of Cu powder and CuI gave better results than the separate use of either one of these. Without copper species, no triarylbismuthanes were formed. Commercial bismuth powder proved to be less satisfactory for

Table 1 Ball-mill synthesis of triarylbismuthanes **2**[a]

	Triarylbismuthane		Reaction time and yield (%)[b]	
2	R¹	R²	6 h	12 h
a	H	H	16	—
b	H	F	41	66
c	F	H	52	81
d	F	F	73	88
e	Cl	H	30	86
f	Br	H	47[c]	83[c]
g	CF_3	H	25	71
h	H	CF_3	29	62
i	$–N{=}CHC_6H_5$	H	25[c]	48[c]
j	NO_2	H	16[d]	—
k	OCH_3	H	30[c]	61[c]
l	$CO_2C_2H_5$	H	27[c]	30[c]
m	3-Pyridyl	H	0	—
n	CN	H	0	—

[a] All new compounds gave satisfactory spectral data and analysis. [b] Yield refers to the isolated compound before recrystallization, unless otherwise noted. No effort was made to optimize the milling conditions. [c] Estimated by ¹H-NMR. [d] Reaction time was 3 h. Prolonged reaction led to extensive decomposition, giving 2,2’-dinitrobiphenyl and unidentified products.

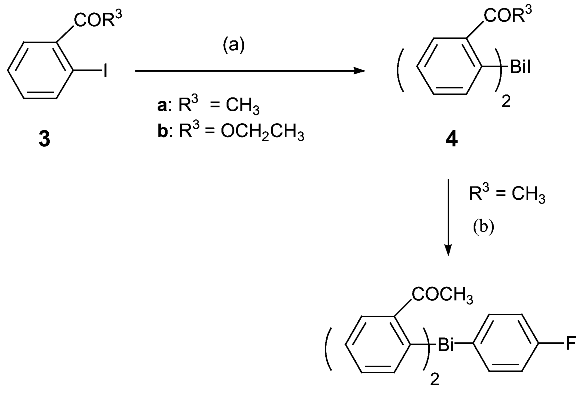
the present purpose. This observation demonstrates a crucial role of the nascent bismuth surface in the formation of organobismuth compounds. Thus, with an idea to modulate the milling rate of bismuth shots, about 0.5–0.7 molar equivalents of calcite grains were added to the reaction mixture, since both bismuth and calcite are located at grade 3 on the Mohs hardness scale. This minor modification improved the results considerably. Of course, too many calcite grains can work adversely toward the formation of organobismuth compounds.

Typically, commercial bismuth shots and calcite grains were placed together with small stainless balls in a stainless vial with a screw cap. Aryl iodide **1**, bearing an electron-withdrawing group at the *ortho* position, commercial Cu powder and CuI were introduced into the vial in an approximate molar ratio 2 : 4 : 3, and the mixture was shaken using a laboratory ball-mill at a rate of 30 Hz for 6–12 h at rt. The resulting dark powdery mass was extracted with benzene by trituration. The extract was filtered on a thin bed of Celite and evaporated to leave a residue, which was recrystallized from ethanol or hexane to give the corresponding triarylbismuthane **2**. The results are summarized in Table 1.

Of special interest is the case where a keto or an ester group occupies the *ortho* position of aryl iodides. The first and second arylation of bismuth occurred smoothly, but it became slow at third stage to produce diaryliodobismuthane **4a,b** as the major product (Scheme 2). In contrast to ordinary diaryliodobismuthanes which readily decompose in wet air, compounds **4a,b** were stable enough to be stored indefinitely on the shelf. Such unexpected high stability of the iodine–bismuth bond in **4** may be explained in terms of the coordinative interaction between the carbonyl oxygen and the bismuth atom.[7] With compound **4a** in hand, unsymmetrically functionalized triarylbismuthane **5** was readily obtained in moderate yield using the same methodology. Symmetrical bismuthane **2b** was not detected in the product mixture.

Though the mechanism is not clear at present, it is highly probable that the reaction proceeds by way of the initial formation of an arylcopper species, which would undergo ligand exchange with a bismuth atom on the new metal surface, eventually leading to triarylbismuthanes *via* either stepwise arylation of bismuth or disproportionation of some arylbismuth species. Since the reaction did not take place in the presence of $BiCl_3$, a possible role of BiI_3 as a partner for arylation may be excluded. Chemical activation of metals has been widely employed in organic synthesis. However, mechanical activation of metals has been investigated mainly from a physicochemical point of view, and only a few attempts have so far been made to exploit it in organic transformations.[8]

In summary, we have developed a novel methodology for the synthesis of *ortho*-functionalized triarylbismuthanes based on the ball mill technique. Though limited in scope at present,[9] the reaction can be carried out in a one-pot reaction under completely dry and neutral conditions, work-up procedure is simple, and product yield is satisfactory.



Scheme 2 *Reagents and conditions:* (a) Bi, CuI, Cu, $CaCO_3$, ball mill, rt; (b) **1b**, Bi, CuI, Cu, $CaCO_3$, ball mill, rt, 6 h.

Notes and references

† *Representative procedure*: 2,4-difluoroiodobenzene **1d** (68.5 mg, 0.285 mmol), Bi shots (0.857 g, 4.10 mmol; Kishida, *ca*. 1 mm in size; 99.999% purity), calcite grains (19.0 mg, 0.190 mmol; 1–3 mm in size),‡Cu powder (35.9 mg, 0.565 mmol), CuI (75.8 mg, 0.398 mmol) and two stainless balls of 7 mm diameter were placed in a stainless vial (1.2 × 4 cm; inside vol. 5 mL). The mixture was shaken at a rate of 30 Hz on a laboratory ball mill (Retsch mixer mill, MM200; Retsch GmbH, Haan, Germany). The reaction vessel warmed slightly by mechanical friction. After 10 h when **1d** had almost disappeared, milling was stopped and the resulting gray to near black powdery product was extracted with benzene (10 mL × 3) by trituration. The combined extracts were filtered on a thin Celite bed and evaporated under reduced pressure to leave crude tris(2,4-difluorophenyl)bismuthane **2d** (46.0 mg, 88%), which was further purified by recrystallization from ethanol to give a pure product as colorless needles, mp 100–101 °C.

‡ A crystalline block of Iceland spar, a transparent variety of calcite from Kansu, China, was purchased from Nichika Corporation, Nakagyo-ku, Kyoto 604–0943, Japan. It was hammered into small pieces of 1–3 mm in size prior to use.

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9 The mechanical performance of our ball mill was fixed. If we could modify the milling efficiency according the reactivity of aromatic iodides employed, the reaction time could be shortened and the yield may be improved further.