Tetrahedron Letters 53 (2012) 2662-2666

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed cross-couplings of functionalized 2-bromobenzofurans for atom-economic synthesis of 2-arylbenzofurans using triarylbismuth reagents

Maddali L. N. Rao*, Dheeraj K. Awasthi, Jalindar B. Talode

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India

ARTICLE INFO

Article history: Received 10 February 2012 Revised 16 March 2012 Accepted 20 March 2012 Available online 24 March 2012

Keywords: 2-Bromobenzofuran Triarylbismuths Palladium catalysis Cross-couplings Atom-economic

ABSTRACT

The palladium catalyzed, atom-economic synthesis of various functionalized 2-arylbenzofurans was achieved through cross-coupling reaction of 2-bromobenzofurans with triarylbismuth reagents. The palladium catalytic protocol is very efficient to furnish various cross-coupled functionalized 2-arylbenzofurnas in high yields using triarylbismuth reagents with three aryl couplings as multi-coupling organome-tallic nucleophiles in one-pot operation. All the coupling reactions were completed in 1 h short reaction time involving three couplings from triarylbismuths under heating condition.

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Benzofurans are important class of biologically active oxygen heterocycles and are present in many natural products.^{1,2} Some of these compounds have been known to exhibit anti-inflammatory,³ antitumor,⁴ anticancer,^{4,5} lipoxygenase inhibitors⁶, and anti-fungal⁷ properties. 2-Aryl substituted benzofuran skeletons are immensely present in the natural products such as cicefuran,⁷ ailanthoidol,⁸ eupomatinoids family,⁹ obovaten¹⁰ etc. with several medicinal applications.

Transition metal mediated cross-coupling methods provide efficient routes for the synthesis of functionalized benzofurans¹¹ which compliment the traditional synthetic methods.¹² For example, Widdowson and co-workers have synthesized Moracin M through cross coupling of 2-stannylbenzofuran with a 5-iodoresorcinolbis(triisopropylsilyl) ether.¹³ Similarly, Lee and co-workers have reported the synthesis of Ailanthoidol by Stille cross-coupling of 2-bromobenzofuran with aryltin reagent under palladium catalyzed conditions.¹⁴ This coupling methodology generally provides the desired ease and flexibility in terms of choosing the appropriate organometallic reagent¹⁵ as nucleophilic partner in combination with a suitable organic electrophile. Thus, various coupling reactions of heteroaryl organometallic nucleophile couplings such as 2-benzo-furanylboronic acids,^{15a,b} 2-benzofuranyltrifluoroborates,^{15c} or 2-benzofuranyldimethylsilanolate^{15d} etc. with aryl halides have been reported under palladium catalysis.

However, some of these heteroaryl organometallic nucleophiles suffer from the problems of stability for efficient couplings.

However, the alternate approach involving 2-halobenzofuran couplings¹⁶ with aryl organometallic nucleophiles is advantageous as the corresponding 2-halobenzofurans and aryl organometallic reagents are easily available with long shelf lives. For example, very recently Lautens and co-workers reported the preparation of 2-bromobenzofurnas using intramolecular cyclizations of orthohydoxy-gem-dibromovinyl benzenes under metal catalyzed conditions.¹⁷ Another method of similar cyclization utilizing TBAF was also been reported.¹⁸ With this background, it was of interest to explore the potential reactivity of triarylbismuth reagents for the synthesis of 2-arylbenzofurans under palladium catalyzed conditions. This is in light of the recent surge in the utility of triarylbismuths as non-toxic, atom-economic, and multi-coupling reagents involving three aryl couplings from each triarylbismuth unit under metal catalyzed conditions.¹⁹ Triarylbismuths are stable compounds and can be easily prepared by the known procedures.²⁰

Herein, we report the atom-economic synthesis of 2-arylbenzofurans under palladium catalyzed couplings of 2-bromobenzoufrans using triarylbismuths as multi-coupling organometallic nucleophiles.

The coupling reaction of 2-bromobenzofuran was studied with triphenylbismuth as organometallic nucleophile under different conditions to establish a viable palladium protocol for this reaction. The screening was conducted with 3.3 equiv of 2-bromobenzofuran with 1 equiv of triphenylbismuth as our aim was to cross-couple three phenyl groups from bismuth reagent to obtain 3 equiv of





^{*} Corresponding author. Tel./fax: +91 512 2597532. E-mail address: maddali@iitk.ac.in (Maddali L. N. Rao).

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 Table 1

 Screening conditions^{a,b,c,d,e,f}



^a Conditions: BiPh₃ (1 equiv), 2-bromobenzofuran (3.3 equiv), base (3 equiv), Pd catalyst (0.1 equiv), PPh₃ (0.4 equiv), solvent (3 mL), 90 °C, 1 h.

^b Isolated yields.

^c Reaction with 4 equiv of Cs₂CO₃.

^d Reaction with 2 equiv of Cs_2CO_3 .

e GC conversion.

^f Homo-coupled biphenyl from BiPh₃ was formed as minor side product. The amount varied with respect to the degree of the cross-coupling product.

2-phenylbenzofuran stoichiometrically. Hence, the investigation was carried out with different catalysts, bases, solvents, and temperature conditions to check their efficacy to deliver the optimum protocol with high cross-coupled product yield of 2-phenylbenzofuran (Table 1).

We have initially employed the routinely used catalyst precursor and phosphine ligand such as $Pd(OAc)_2$ and triphenylphosphine for this study with different bases in *N*-methylpyrrolidone (NMP) solvent under heating condition (Table 1, entries 1-5). This attempt furnished varied amounts of cross-coupled product yields. For example, the coupling reaction with K₂CO₃, KOAc, and Cs₂CO₃ yielded 76%, 71%, and 96% respectively. The reactions with Na₂CO₃ and K₃PO₄ gave 53–54% yields. Formation of biphenyl as a minor side product from triphenylbsimuth was observed and this is a known reactivity of triarylbismuth to give homo-coupling product under metal catalysis.²¹ From this study, Cs₂CO₃ base clearly emerged as a better choice with excellent yield. This prompted us to check the efficacy of different palladium catalysts (Table 1, entries 6–9). In this investigation, although $PdCl_2(PPh_3)_2$ and Pd(PPh₃)₄ fared reasonably well with 70% and 72% yields, other catalysts were found to be ineffective. Thus, further investigation in different solvents was carried out with Cs₂CO₃ base and Pd(OAc)₂/ PPh₃ system (Table 1, entries 10–13). However, this study did not provide any better outcome as the solvents such as N.N-dimethylacetamdie (DMA), N,N-dimethylformamide (DMF), THF, and 1,4dioxane delivered yields up to 22-53%. Furthermore, use of different amounts of Cs₂CO₃ base in four and 2 equiv along with no base condition as control experiments provided 85%, 73%, and 19% yields, respectively (Table 1, entries 14-16). This also established that 3 equiv of Cs₂CO₃ is sufficient to obtain high cross-coupling vield (Table 1, entry 5). Additional check at varied temperature conditions between 30,40 and 60 °C found to be not suitable for effective coupling (Table 1, entries 17-19). Further study without catalyst and ligand did not furnish the desired product (Table 1, en-

Table 2

Cross-couplings of 2-bromobenzofuran with different BiAr3^{a,b,c,d}



(continued on next page)

Table 2 (continued)



^a Reaction conditions: 2-bromobenzofuran (0.825 mmol, 3.3 equiv), BiAr₃ (0.25 mmol, 1 equiv), Pd(OAc)₂ (0.025 mmol, 0.1 equiv), PPh₃ (0.1 mmol, 0.4 equiv), Cs₂CO₃ (0.75 mmol, 3 equiv) and NMP (3 mL), 90 °C, 1 h. ^b Isolated yields calculated considering all three aryl groups of BiAr₃ for coupling. Thus, 0.75 mmol of the product correspond to 100% yield.

^c Homo-coupled bi-aryls from triarylbismuths formed in all the reactions in minor amounts.
 ^d All products were characterized by ¹H NMR, ¹³C NMR, IR, and ESI-HRMS data and in comparison with the literature data.

Table 3

Cross-couplings of substituted 2-bromobenzofurans with different $\operatorname{BiAr_3}^{a,b,c,d}$



Table 3 (continued)

Entry	BiAr ₃	2-Bromobenzofuran	2-Arylbenzofuran		Yield (%)
11		.,		3.11	88
12	Ві-	Br Br	Br	3.12	90
13	BiMe)3		BrMe	3.13	87
14	Bit CI		Br	3.14	85
15	Bit F		Br	3.15	88
16	Bi OMe	.,	Br OMe	3.16	91
17	Bi	'n	Br OEt	3.17	93
18	Bi	OMe Br		3.18	86
19	Bi-Me		OMe Me	3.19	83
20				3.20	80
21	Bi-(F)3		OMe	3.21	84
22	Bi-OMe)		OMe OMe	3.22	81
23	Bi-OEt)3		OMe	3.23	86

^a Reaction conditions: 2-bromobenzofuran (0.825 mmol, 3.3 equiv), BiAr₃ (0.25 mmol, 1 equiv), Pd(OAc)₂ (0.025 mmol, 0.1 equiv), PPh₃ (0.1 mmol, 0.4 equiv), Cs₂CO₃ (0.75 mmol, 3 equiv) and NMP (3 mL), 90 °C, 1 h.

^b Isolated yields calculated considering all three aryl groups of BiAr₃ for coupling. Thus, 0.75 mmol of the product correspond to 100% yield.

^c Homo-coupled bi-aryls from triarylbismuths formed in all the reactions in minor amounts.

^d All products were characterized by ¹H NMR, ¹³C NMR, IR, and ESI-HRMS data and in comparison with the literature data.

try 20). From this systematic investigation, the coupling conditions involving BiPh₃ (1 equiv), 2-bromobenzofuran (3.3 equiv), Pd(OAc)₂ (0.1 equiv), PPh₃ (0.4 equiv), and Cs₂CO₃ (3 equiv) in NMP at 90 °C for 1 h evolved as an optimized protocol to obtain high cross-coupled yield (Table 1, entry 5).

muth to yield high cross-coupling product under the established protocol conditions. The observed coupling reactivity is superior in comparison to the literature methods reported for such couplings with other organometallic reagents.^{14,16}

The coupling reactivity of 2-bromobenzofuran witnessed with $BiPh_3$ as a model reaction is heartening from the view point that the overall coupling conditions involve only 1 h reaction time comprising three aryl couplings from bismuth reagent. This denoted

the facile reactivity of both 2-bromobenzofuran and triphenylbis-

Table 2, the reactivity of different triarylbismuths demonstrated high coupling ability with overall 80–96%, cross-coupled yields.²² Both electronically rich and deficient triarylbismuth reagents demonstrated high reactivity with three aryl transfers for cross-coupling purpose in a short reaction time and is an important point to note in these couplings.

Furthermore, the generality of these couplings with different 2-bromobenzofurans and triarylbismuths was established under optimized conditions²² and the results are given in Table 3. The coupling reactions of variously substituted 2-bromobenzofurans with electronically different groups such as 5-acetyl, 5,7-dichloro, 5-bromo, and 7-methxoy reacted well to furnish the corresponding functionalized 2-arylbenzofuans in combination with different triarylbismuths in excellent yields. The coupling reactions with 2,5-dibromobenzofuran reacted regioselectively at 2-position. The reactivity of 2-bromo-5,7-dichlorobenzofuran was also found to be similar and coupling underwent at 2-position furnishing the corresponding 2-arylbenzofuran in high yields.

The cross-coupling reactivity demonstrated in this study is highly productive and led to the formation of 2-arylbenzofurans in excellent yields in 1 h short reaction time. This is in sharp contrast to the reactivity earlier reported using aryl organometallic reagents. For example, the coupling reaction involving one C–C bond formation using 2-bromobenzouran and aryltin reagents required heating at 145 °C for 5 h.14 Similar couplings using aryl boronic acids^{16b,c} reacted under reflux conditions and long hours some times. The coupling reaction of 2-bromobenzofuran was reported with *n*-Bu₃Bi at 110 °C which needed 18 h for one alkyl coupling from trialkylbismuth reagent.²³ The present aryl coupling method with triarylbismuths is advantageous from various counts such as three aryl couplings in atom-economic manner in one-pot operation, faster reactivity in shorter reaction times, high coupling vields, and utilization of non-toxic bismuth reagents as organometallic nucleophiles under palladium catalyzed conditions.

In summary, we have demonstrated atom-economic synthesis of 2-arylbenzofurans from the cross-coupling reaction of 2-bromobenzfurans with triarylbismuth reagents under palladium catalytic protocol conditions. This methodology with several advantages is expected to provide a facile platform in synthetic organic chemistry for the synthesis of a plethora of 2-arylbenzofurans in high yields.

Acknowledgments

We greatfully acknowledge the financial support received from the Department of Science and Technology (DST), New Delhi for this work through Green Chemistry program (DST No. SR/S5/GC-11/2008). D.K.A. and J.B.T. thank the University Grants Commission (UGC) New Delhi, respectively for research fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03. 059.

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- 22. Representative cross-coupling procedure: In a hot oven-dried Schlenk tube under N₂ atmosphere were added Ph₃Bi (0.25 mmol, 110 mg, 1.0 equiv), 2-bromobenzofuran (0.825 mmol, 163 mg, 3.3 equiv), Cs₂CO₃ (0.75 mmol, 244 mg, 3.0 equiv), Pd(OAc)₂ (0.025 mmol, 5.6 mg, 0.1 equiv), Pd(), Pd(), 0.025 mmol, 5.6 mg, 0.1 equiv), Pd(), 0.1 mmol, 26 mg, 0.4 equiv), and NMP (3 mL) solvent. The resulting mixture was stirred in preheated oil bath at 90 °C for 1 h. After the reaction is over, the mixture was cooled, quenched with dil HCl and extracted with ethyl acetate. The combined organic extract was washed with water, brine, and dried over MgSO₄ and concentrated. The crude was subjected to silica gel column chromatography (230–400 mesh) using petroleum ether as the eluent to obtain the pure 2-phenylbenzofuran (**2.1**) as a white solid (140 mg, 96%). The product was characterized by spectroscopy and in comparison with the literature data.
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