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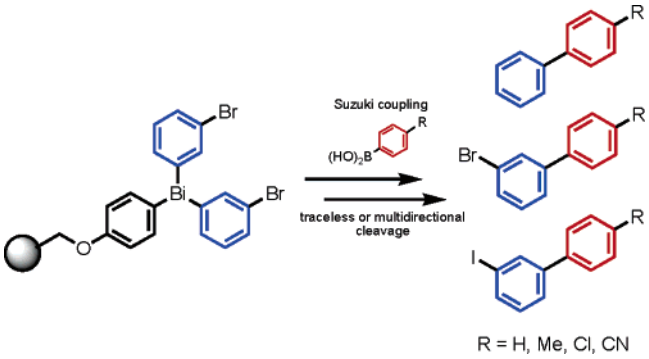
Solid-Phase Synthesis with Resin-Bound Triarylbismuthanes: Traceless and Multidirectional Cleavage of Unsymmetrical Biphenyls†

L. Kyhn Rasmussen,‡ Mikael Begtrup,‡ and Thomas Ruhland*

Department of Medicinal Chemistry, H. Lundbeck A/S, 9 Ottiliavej, DK-2500 Valby, Denmark

tr@lundbeck.com

Received August 26, 2005

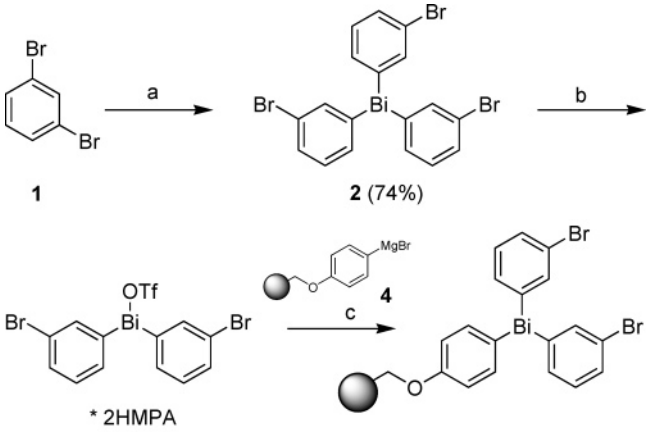


A multistep solid-phase organic synthesis with resin-bound bismuth linker is described. The flexibilities inherent in this system through novel chemoselective cross-coupling reactions, in conjunction with multidirectional and/or traceless cleavage methodologies, are exploited.

The availability of flexible synthetic methodologies is paramount in modern synthetic chemistry. In recent years, intensive research efforts have been directed toward increasing flexibility in solid-phase organic synthesis (SPOS) through new linker concepts. In the field of drug discovery research, traceless- and multidirectional-linker strategies are particularly attractive for the design of small biologically active molecules. SPOS with a traceless linker allows the synthesis of target molecules devoid of a "memory" of their former attachment point, and SPOS with a multidirectional linker enables the introduction of different functionalities by means of varied cleavage methods.[1−3]

In a previous report we demonstrated the use of resin-bound bismuth as an arylation reagent and as a multidirectional linker.[4] However, multistep synthesis on resin-bound bismuthanes has not been described previously. The use of resin-bound bismuth in SPOS requires that chemical transformations can be performed prior to cleavage without debismuthylation. Functionalization of triarylbismuthanes at the aryl groups has only been studied sparsely in solution phase.[5,6] We now report the first application of resin-bound arylbismuthanes in SPOS using the Suzuki cross-coupling reaction.[7] We demonstrate that immobilization of bismuthanes enables chemoselective palladium-catalyzed cross-coupling reactions that would be difficult or impossible to perform in solution phase. In addition, we show that degradation of resin-bound triaryl bismuthanes can be directed to create either a sp^2C-halogen bond (multidirectional cleavage) or a sp^2C-H bond (traceless cleavage). This approach leads to functionalized biphenyl frameworks of pharmaceutical interest.[8] Han et. al. have reported a convenient multidirectional and traceless SPOS synthesis of biphenyls using resin-bound silicon.[9] However, the bismuth linker offers additional possibilities for multidirectional cleavage in comparison to the silicon linker.[4] Furthermore, the bismuth linker carries two aryl groups that are both utilized in product formation.

SCHEME 1. Synthesis of Resin-Bound Bismuthane 5[a]



[a] Reagents and conditions: (a) (i) 0.9 equiv of *n*-BuLi, THF, −78 °C 1.5 h; (ii) 0.3 equiv of $BiCl_3$, −78 °C to rt over 1−3 h, then rt overnight; (b) 1 equiv of TMSOTf, 2 equiv of HMPA, MeOH/DCM, 0 °C to rt over 1 h; (c) THF, 0 °C, then rt overnight.

The resin-bound bismuthane **5** was prepared as shown in Scheme 1. Bromine−lithium exchange was carried out on 1,3-dibromobenzene **1** using *n*-butyllithium. Subsequent treatment with trichlorobismuthane furnished tris(3-bromophenyl) bismuthane **2** in 74% yield. The bismuthane **2** was quantitatively converted into the corresponding bis(3-bromophenyl)bismuth triflate 2*HMPA complex **3** using the procedure developed by Suzuki et al.[10−12] As expected, complex **3** smoothly bismuthy-

* To whom correspondence should be addressed. Ph: +45 3643 3304. Fax: +45 3643 8237.

† Dedicated to Prof. Dr. P. Knochel on the occasion of his 50th birthday.

‡ The Danish University of Pharmaceutical Sciences, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

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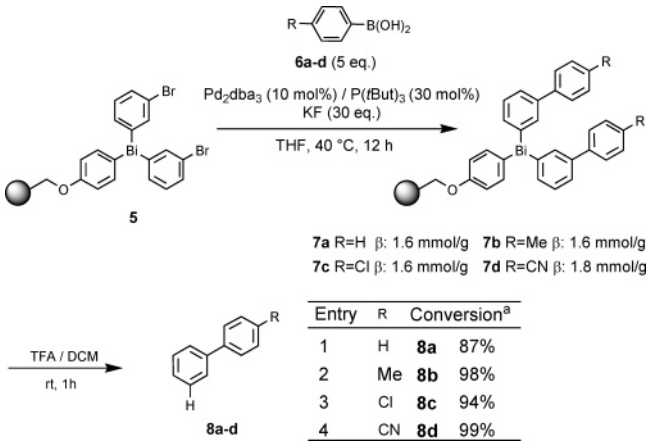
10.1021/jo051803d CCC: $33.50
Published on Web 01/07/2006

SCHEME 2. Suzuki Cross-Coupling of Resin-Bound Bromophenylbismuthane 5 and Aryl Boronic Acids[a]



Entry	R	Conversion[a]	
1	H	**8a**	87%
2	Me	**8b**	98%
3	Cl	**8c**	94%
4	CN	**8d**	99%

[a] Conversion of resin-bound bis(bromophenyl) bismuthane **5** to biphenyls after 12 h was determined by standardized GC−MS after cleavage from the resin by treatment with TFA/CH_2Cl_2 (1:1) at rt for 1 h. "Conversion" represents the relative amounts of bromobenzene and biphenyls after cleavage.

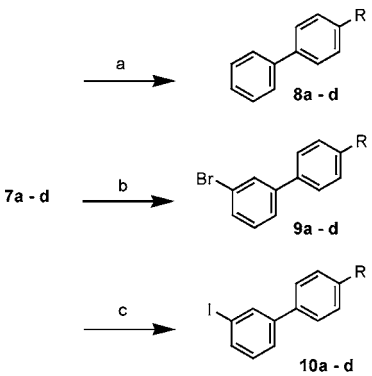
lated resin-bound aryl Grignard reagent **4**, affording the resin-bound bismuthane **5** with a loading of 1.9 mmol/g (based on Br).[4]

Both, triarylbismuthanes and boronic acids, act as donors in palladium-catalyzed cross-coupling reactions with arylbromides.[13,14] Therefore, a chemoselective cross-coupling reaction with arylbromides in the presence of both, a triarylbismuthane and a boronic acid, would be difficult or even impossible in solution phase. However, immobilization of the bromophenyl bismuthane on solid phase prevents the bismuthane from coupling with the resin-bound aryl bromide.

Mild reaction conditions were required for the Suzuki coupling reaction in order to suppress side reactions of the immobilized bismuthane. Therefore, different solvents, palladium sources, ligands, and promoters were screened. With tetrahydrofuran as solvent, with the combination of Pd_2dba_3 and tri-*tert*-butylphosphane as catalyst, and with potassium fluoride as promoter, satisfactory conversion was obtained at 40 °C within 12 h (Scheme 2). It was found that the solid-phase approach required larger amounts of palladium catalyst and promoter than similar cross-coupling reactions in solution.[15] We also compared the performance of different boronic acid derivatives. Phenyl boronic acid performed better (87% conversion) than its 1,3-propanolate derivative (51% conversion), whereas with potassium phenyl trifluoroborate no conversion was observed.

The biphenyls were cleaved by halo-debismuthylation from the resin-bound bismuthanes by treatment with a solution of iodine or bromine in tetrahydrofuran or dichloroethane, respectively (Table 1, entries 5−12). The halogen-substituted biphenyls

TABLE 1. Cleavage of Biphenyls from Resin 7a−d[a]



Entry:	Product:	R:	Yield:[b]
1	**8a**	H	68%
2	**8b**	Me	59%
3	**8c**	Cl	58%
4	**8d**	CN	62%
5	**9a**	H	62%
6	**9b**	Me	48%
7	**9c**	Cl	83%
8	**9d**	CN	77%
9	**10a**	H	60%
10	**10b**	Me	69%
11	**10c**	Cl	66%
12	**10d**	CN	65%

[a] Reagents and conditions: (a) TFA/CH_2Cl_2 (1:1), rt, 1 h; (b) 2 equiv of Br_2, CH_2Cl_2, 60 °C,12 h; (c) 2 equiv of I_2, THF, 60 °C, 12 h. [b] Isolated yields of analytically pure biphenyls after purification by column chromatography.

were obtained in isolated yields from 48% to 83% over two steps (calculated from starting resin **5**). Halo-debismuthylation takes place through three repetitive cycles of oxidation of Bi^{III} by halogen to Bi^{V} and subsequent reductive elimination.[16−19]

Traceless cleavage was performed using TFA/CH_2Cl_2 (1:1) at room temperature and afforded the biphenyls in yields from 58% to 68% over two steps (Table 1, entries 1−4). The mechanism of proto-debismuthylation is not known in detail but is probably similar to that of proto-desilylation.[20] In comparison to resin-bound silicon, traceless cleavage from resin-bound bismuth seems to give significantly higher yields.[9] As mentioned earlier, both aryl groups of the bismuth linker can be utilized in product formation, resulting in a high resin loading.[21,22]

Functionalized biphenyls of potential pharmaceutical interest have been synthesized using a chemo-selective Suzuki cross-coupling reaction followed by multidirectional or traceless cleavage with bromine, iodine, or trifluoroacetic acid from resin-bound bismuthanes. Substituted biphenyls were obtained in moderate to good overall yields over two steps. To the best of our knowledge this report is the first use of resin-bound bismuth in SPOS and the first example of a solid-phase strategy for the achievement of chemo-selective cross-coupling reactions. In addition, halo- and proto-debismuthylation reactions have been used for the first time as synthetically useful tools.[23] We would also like to emphasize that dimetalated arenes, such as the resin-bound bismuth−palladium arene intermediate, have rarely been reported in the literature.[24]

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Experimental Section

General Procedure for Suzuki Cross-Coupling of Resin 5. Synthesis of 7a. To a suspension of resin **5** (2.0 g, 3.7 mmol) in THF (20 mL) were added phenylboronic acid (1.1 g, 9.3 mmol), potassium fluoride (3.2 g, 56 mmol), tris(dibenzylideneacetone)-dipalladium (0.17 g, 0.19 mmol), and tri-*tert*-butylphosphane (0.11 g, 0.56 mmol). The reaction was heated to 40 °C for 12 h. The resulting resin was filtered through a sintered glass filter (G3) and washed with THF (3 × 10 mL), H_2O (3 × 10 mL), MeOH−H_2O 1:1 (3 × 10 mL), THF−H_2O 1:1 (3 × 10 mL), THF (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL) and dried overnight at 40 °C in vacuo to give **7a** as a black resin. Calculated from gain in weight resin **7a** had a loading of 1.6 mmol/g. Resins **7b**−**d** were prepared analogously.

General Procedure for Traceless Cleavage with TFA. Synthesis of Biphenyl 8a. To a suspension of resin **7a** (0.30 g, 0.48 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (1 mL). The suspension was stirred for 12 h at room temperature. The resin was filtered and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. The crude product was concentrated in vacuo and purified by column chromatography (heptane) to yield 49 mg (68%) of **8a** as a solid, mp 66.5−67.7 °C. ^{1}H NMR ($CDCl_3$) δ: 7.4 (2H, t, J = 7.1 Hz), 7.4 (4H, t, J = 7.5 Hz), 7.6 (4H, d, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 126.1, 126.2, 127.7, 140.2. Biphenyls **8b**−**d** were prepared analogously.

General Procedure for Cleavage with Bromine. Synthesis of 3-Bromobiphenyl 9a. To a suspension of resin **7a** (0.50 g, 0.80 mmol) in dichloroethane (10 mL) was added bromine (0.50 g, 3.2 mmol). After stirring at 60 °C for 12 h, the reaction was filtered. The resin was extracted with CH_2Cl_2 (2 × 5 mL) and THF (2 × 5 mL). To the combined organic phases was added aqueous $Na_2S_2O_3$ (1 M, 5 mL), the organic solvents were removed in vacuo, and to the residue were added H_2O (20 mL) and EtOAc (20 mL). The phases were separated, and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. The crude product was concentrated in vacuo and purified by column chromatography (heptane) to yield 113 mg (62%) of **9a** as an oil. ^{1}H NMR ($CDCl_3$) δ: 7.3 (1H, t, J = 7.5 Hz), 7.4 (1H, t, J = 7.0 Hz), 7.42−7.48 (3H, m), 7.5 (1H, d, J = 7.5 Hz), 7.6 (2H, t, J = 7.5 Hz), 7.7 (1H, t, J = 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ: 123.3, 126.2, 127.5, 128.27, 129.29, 130.58, 130.63, 130.7, 140.1, 143.7. Biphenyls **9b**−**d** were prepared analogously.

General Procedure for Cleavage with Iodine. Synthesis of 3-Iodobiphenyl 10a. To a suspension of resin **7a** (0.50 g, 0.80 mmol) in THF (10 mL) was added iodine (0.39 g, 1.6 mmol). After stirring at 60 °C for 12 h, the reaction was filtered, and the resin was extracted with THF (3 × 5 mL). To the combined organic phases was added aqueous $Na_2S_2O_3$ (1 M, 5 mL), and the organic solvent was concentrated in vacuo. To the residue were added H_2O (20 mL) and EtOAc (20 mL). The phases were separated, and the aqueous phase extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. The crude product was purified by column chromatography (heptane) to yield 131 mg (60%) of **10a** as viscous oil. ^{1}H NMR ($CDCl_3$) δ: 7.2 (1H, t, J = 8.0 Hz), 7.36 (1H, t, J = 7.5 Hz), 7.43 (2H, t, J = 7.1 Hz), 7.51-7.55 (3H, m), 7.7 (1H, d, J = 8.0 Hz), 7.9 (1H, t, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 95.2, 126.8, 127.5, 128.3, 129.3, 130.8, 136.56, 136.60, 140.0, 143.8. Biphenyls **10b**−**d** were prepared analogously.

Acknowledgment. We thank Dr. Robert Dancer and Ejner K. Moltzen for proofreading the manuscript. The secretarial assistance of Ms. Vibeke Larsen is highly appreciated.

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051803D