Journal of Organometallic Chemistry 694 (2009) 1638–1641

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

No-carrier-added radiohalogenations utilizing organoboranes: The synthesis of iodine-123 labeled curcumin

George W. Kabalka *, Min-Liang Yao

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996-1600, United States

ARTICLE INFO

Article history:
Received 2 October 2008
Received in revised form 17 November 2008
Accepted 18 November 2008
Available online 30 November 2008

Keywords:
Organoborane
Radiohalogenation
Curcumin
Organotrifluoroborate
Amyloid

ABSTRACT

The use of organoborane intermediates for radiohalogenations is briefly reviewed. The synthesis of an iodine-123 labeled curcumin derivative using a newly developed radio-iodination technique is reported.

1. Introduction

The first report of isotope incorporation (tritium) via borane intermediates appeared shortly after Brown's initial report of the hydroboration reaction [1,2]. The emphasis of the early tritiation study was on reaction mechanisms and not on the synthesis of radiolabeled organic molecules. What was clear in the 1960s was that a large variety of functionally substituted organoborane derivatives could be prepared and that they were well tolerated in subsequent reactions in which the boron atom was replaced by other elements and functional groups (Scheme 1). At that time, organoboranes were unique amongst the reactive organometallic and organometalloidal reagents available because they could contain a variety of functions groups while maintaining high reactivity [3].

The realization that one could prepare reactive intermediates containing functional groups led us to investigate the use of organoboranes in isotope-incorporation reactions. Over the years, we successfully developed methods for incorporating short and long lived isotopes of carbon, nitrogen, oxygen, and the halogens (Scheme 2) [4,5].

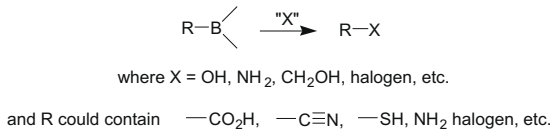
We had established by 1980 that organoboranes could be utilized to incorporate isotopes, but the reactions were not frequently employed. The reason for the apparent lack of interest was that, in general, researchers found the preparation of the prerequisite organoborane reagents to be rather restrictive. Trialkylboranes were accessible via the hydroboration reaction only if the appropriate alkenes were available. The preparation of aromatic borane derivatives was even more problematic in that transmetallation reactions were generally required. The necessity of using reactive (and basic) Grignard and lithium reagents often precluded the presence of interesting and useful functionality in the target molecules.

The situation changed dramatically after Akira Suzuki and Norio Miyaura discovered new palladium catalyzed carbon–carbon and carbon–boron bond forming reaction; the new coupling reactions generally occur at, or near, room temperature in the presence of very mild organic and inorganic bases [6,7]. One only needs to examine a current organic chemistry journal to realize the impact of the palladium catalyzed, boron-based, Suzuki–Miyaura reactions. Due to the importance of the Suzuki reaction, several novel methods for preparing organoboron esters were developed in last decade [8,9]. And these novel methods make it possible to readily introduce a variety of functionality into boronate derivatives.

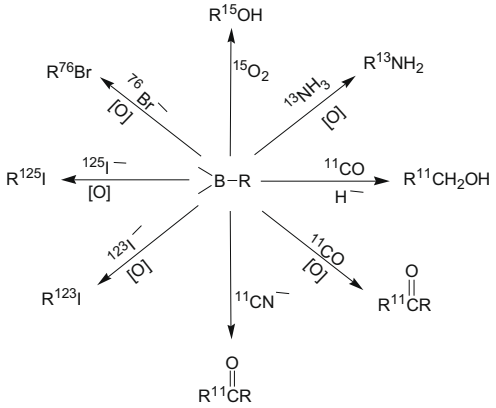
The availability of functionalized boronic acid starting materials and the non-toxic nature of boron served to make boron chemistry attractive to the radiolabeling community. The reactions proceed readily at the no-carrier-added level and tolerate a variety of functional groups. One can find examples of boron reagents being used for the incorporation of carbon-11, nitrogen-13, oxygen-15 [10,11]. Early in 1981, we developed boron-halogen exchange reactions and found them to be ideal precursors (Scheme 3) [12,13]. Radiohalogenations of organoboron compounds also have found wide application in nuclear medicine and biology [4,5,14] due to their ready availability and lack of toxicity. In addition, halogenation of organoboranes has played an important role in organic

* Corresponding author. Tel.: +1 865 9742997.
E-mail address: kabalka@utk.edu (G.W. Kabalka).

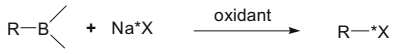
0022-328X/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2008.11.040



Scheme 1.



Scheme 2.



Scheme 3.

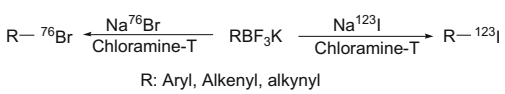
syntheses. For example, it provides a convenient route to substituted haloarene intermediates of medicinal importance that otherwise are not accessible [15–17].

In 1995, Vedejs et al. reported the first preparation of trifluoroborates from boronic acids [18]. The trifluoroborates are remarkably stable when compared to the corresponding boronic acids, exhibiting shelf lives on the order of years under atmospheric conditions. And recent studies involving the trifluoroborate derivatives have demonstrated how the boron reagents themselves tolerate a wide variety of chemical transformations [19]; these include nucleophilic substitution reactions [20], epoxidations [21], Wittig reactions [22], and Click chemistry [23]. The importance of these reports is that they validate the fact that boronated intermediates can "carry" a plethora of pharmaceutically important functional groups late into reaction sequences.

In a continuation of our studies focused on the radiohalogenation of organoboron compounds, we reported that organotrifluoroborates are suitable radiohalogenation precursors (Scheme 4) [24–28]. We have applied the new chemistry to a number of useful agents including our recent synthesis of an iodine-123 labeled refecoxib agent [29] and iodostyrylbenzoxazole [30].

In addition, the facile interconversion [18,31,32] between boronic acids, boronic esters and trifluoroborates is extremely attractive since one can utilize whichever precursor is most effective when considering radiopharmaceutical preparations.

Recent studies suggested that the anti-fibrillogenic and antioxidant effects of curcumin, a non-steroidal and anti-inflammatory



Scheme 4.

compound found in the spice, Turmeric, may be responsible for the low, age-adjusted prevalence of Alzheimer's disease in India (4.4-fold less than that found in the USA) [33]. Several studies reveal that curcumin's anti-fibrillogenic activity involves fibril-binding as well as destabilization and inhibition of fibril growth. In addition, favorable brain permeability and satisfactory Aβ plaque binding properties have been predicted from the fluorescence staining of Aβ plaques in brain sections from APPsw transgenic mice administered curcumin by injection or via their diet [34]. Currently, curcumin is undergoing a Phase II clinical trial in patients with mild to moderate Alzheimer's disease [35]. Because of this, we have synthesized iodine-123 labeled curcumin using our recently developed radiohalogenation technique (Scheme 5) and carried out preliminary binding studies using amyloid fibrils associated with non-Alzheimer's disorders, such as primary (AL) and systemic AA amyloidosis.

2. Results and discussion

The syntheses of trifluoroborate precursor (**4**) and the stable iodinated curcumin (**2**) are shown in Scheme 6. Reported procedures [36] were utilized to prepare compound **2**. The Aldol condensation of vanillin and an acetylacetone–boron complex gave the keto-enol intermediate **1** in 66% yield after column chromatography and recrystallization. In the presence of piperidine, compound **1** coupled readily with 5-iodovanillin to afford the iodocurcumin **2**. Consistent with reported NMR spectra for curcumin and its analogues [37,38], compound **2** gives typical enol resonances at 16.35 ppm (s) and 6.05 ppm (s) in the ^{1}H NMR spectrum. This indicates that the enol form is strongly favored by intramolecular H-bonding in the equilibrium between the diketo and keto-enol forms.

Boron ester **3** was prepared by the reaction of compound **2** with bis(pinocolato)diboron in the presence of $PdCl_2$(dppf) and KOAc. Treatment of crude **3** with 10 equiv. of KHF_2 gives trifluoroborate precursor **4** as a yellow-brown solid.

Radioiodination of trifluoroborate precursor **4** using Na[^{123}I] in the presence of chloramine-T was carried out at room temperature. Radiochemically pure iodine-123 labeled curcumin was isolated in a 15% yield in 40 min. SPECT imaging studies of iodine-123 labeled curcumin in a cohort of 5H-2/huIL-6 transgenic mice with systemic AA amyloidosis are currently underway.

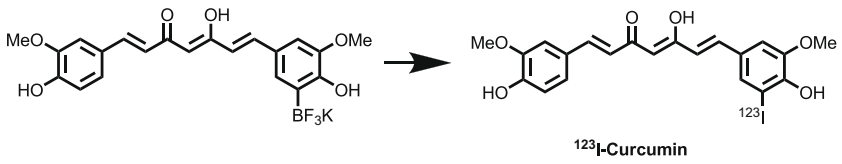
In conclusion, a potential amyloid localizing reagent was successfully prepared using a stable trifluoroborate precursor. The methodology reported is readily amenable to kit applications for the preparation of a wide variety of no-carrier-added radioiodinated amyloid imaging agents.

3. Experimental

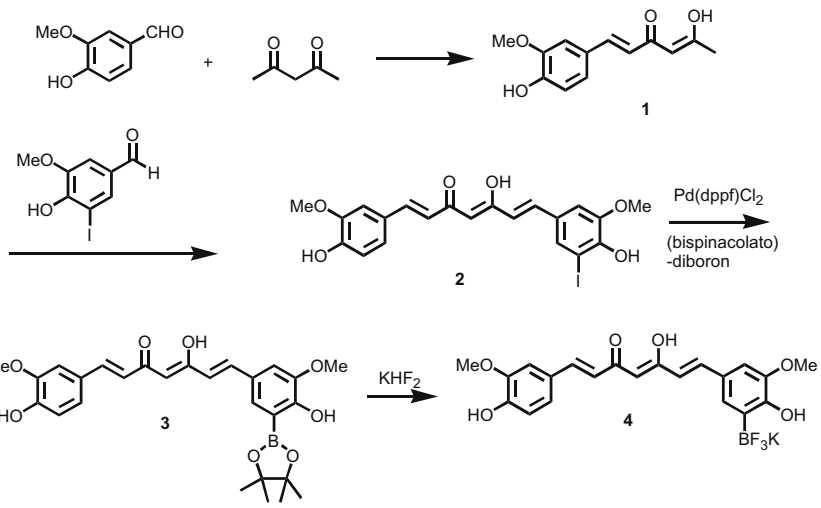
All glassware was dried in an oven at 120 °C and flushed with dry argon. All reactions were carried out under an argon atmosphere. DMSO was distilled over CaH_2. Other reagents were purchased from commercial sources and used as received. Products were purified by flash chromatography using silica gel (60Å, 230–400 mesh). ^{1}H NMR and ^{13}C NMR were obtained utilizing a Bruker 250 MHZ (proton) multinuclear analytical NMR.

3.1. Synthesis of **1**

2,4-Pentanedione (6.0 g, 60 mmol) and B_2O_3 (1.39 g, 20 mmol) were dissolved in ethyl acetate (40 mL) and the solution stirred at 80 °C for 30 min. To this mixture was added vanillin (3.0 g, 20 mmol, dissolved in 40 mL of ethyl acetate) and (n-BuO)$_3$B (4.6 g, 20 mmol). After stirring for 30 min at 80 °C, n-butylamine (1.46 g, 20 mmol) was added dropwise to the mixture which was



Scheme 5.



Scheme 6.

allowed to stir at 100 °C for 1 h. The mixture was then treated with 1 N aqueous HCl (10 mL) at 50 °C and stirred at that temperature for 30 min. The mixture was extracted with ethyl acetate, washed with water, and then dried over anhydrous Na_2SO_4. Flash column chromatography (3:1 hexanes–ethyl acetate), followed by recrystallization from ethanol and water, gave **1** (3.1 g, 66%) as a yellow solid. ^{1}H NMR ($CDCl_3$): 15.5 (s, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.11–6.91 (m, 3H), 6.33 (d, J = 15.6 Hz, 1H), 5.89 (s, 1H), 5.63 (s, 1H), 3.94 (s, 3H), 2.16 (s, 3H).

3.2. Synthesis of *2*

5-Iodovanillin (1.7 g, 6.0 mmol) and B_2O_3 (690 mg, 10 mmol) were dissolved in ethyl acetate (10 mL) at 80 °C, and to this mixture was added an ethyl acetate solution (10 mL) of **1** (1.17 g, 5.0 mmol) and (n-BuO)$_3$B (2.3 mL, 10 mmol). After stirring for 30 min, the mixture was treated with piperidine (170 mg, 2.0 mmol) at 80 °C for 30 min and then with 0.4 N aqueous HCl (7 mL) at 50 °C for 30 min. The reaction mixture was extracted with ethyl acetate. Removal of the solvent gave a dark brown solid. After washing with hot water (200 mL) and then hot methanol (50 mL), an orange solid (1.8 g, 73%) was obtained. (*Note*: The NMR spectrum of compound **2** is different from the reported one given in Ref. [36]).

^{1}H NMR (DMSO-d_6): 16.35 (s, br, 1H), 10.11 (s, 1H), 9.66 (s, 1H), 7.65–6.71 (m, 9H), 6.05 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (DMSO-d_6): 183.8, 182.4, 149.4, 148.5, 148.0, 147.2, 141.2, 138.9, 131.4, 128.3, 126.3, 123.0, 122.3, 120.9, 115.7, 111.5, 100.9, 84.7, 56.3, 55.7.

3.3. Synthesis of *3*

Into a 50 mL dried round-bottomed flask was added $PdCl_2$(dppf) (11.5 mg, 0.016 mmol), KOAc (154 mg, 1.57 mmol), and (bispinacolato)diboron (145 mg, 0.57 mmol). The flask was flushed with argon and then charged with dry DMSO (5 mL). After stirring for 15 min, compound **2** (256 mg, 0.52 mmol, dissolved in 5 mL DMSO) was added to the reaction mixture. The mixture was heated at 80 °C for 20 h and then cooled to room temperature. After removal of the solvent under vacuum, followed by washing sequentially with water and ethyl acetate, crude **3** was obtained**.** Due to its very poor solubility, the NMR of compound **3** was not obtained.

3.4. Synthesis of compound *4*

Crude **3** (obtained as described above), DMF (10 mL), and methanol (10 mL) were added to a round-bottomed flask and cooled to 0 °C. To this mixture, a KHF_2 (0.40 g, 5.2 mmol) solution in water (8 mL) was added dropwise. The mixture was stirred at room temperature for 12 h. Removal of the solvents under vacuum, followed by washing sequentially with water (10 mL) and methanol (3 mL), yielded crude **4** as a yellow-brown solid. Due to its very poor solubility, the NMR of compound **4** was not obtained and it was used directly in the next step.

3.5. Preparation of the Iodine-123 labeled *2*

A solution of **4** (100 μL of 5.2×10^{-3} M solution in 50% aqueous THF) was placed in a 2 mL Wheaton vial containing no-carrier-added $Na^{123}I$ (37 M Bq in 0.1% aqueous NaOH). Chloramine-T (1.0 mg) was added to the reaction vial which was sealed and covered with aluminum foil. The reaction mixture was stirred for 15 min at room temperature and then aqueous sodium thiosulfite (100 μL of a 1.0×10^{-4} M solution) was added to destroy residual molecular iodine. The crude radiolabeled product was isolated by passing it through a silica gel cartridge using ethyl acetate as eluant. The total synthesis time was about 40 min. The radiochemical yield was 15%.

Acknowledgements

Acknowledgement is made to the US Department of Energy, the Robert H. Cole Foundation, and Physician's Medical Education and Research (PMERF).

References

[1] H.C. Brown, B.C. Subba Rao, J. Am. Chem. Soc. 78 (1956) 5694.
[2] N.H. Nam, A.J. Russo, R.F. Nystrom, Chem. Ind. (London) (1963) 1876.
[3] H.C. Brown, Boranes in Organic Chemistry, Cornell University Press, Ithaca, NY, 1972.
[4] G.W. Kabalka, Acc. Chem. Res. 17 (1984) 215.
[5] G.W. Kabalka, J. Labelled Compd. Radiopharm. 50 (2007) 888.
[6] N. Miyaura, A. Suzuki, Chem. Rev. 95 (1995) 2457.
[7] A. Suzuki, J. Organomet. Chem. 576 (1–2) (1999) 147.
[8] G.W. Kabalka, B.C. Das, S. Das, Tetrahedron Lett. 43 (2002) 2323.
[9] T.M. Boller, J.M. Murphy, T. Ishiyama, N. Miyaura, J.F. Hartwig, J. Am. Chem. Soc. 127 (2005) 14263.
[10] G.W. Kabalka, G.W. McCollum, A.S. Fabrikiewitz, R.M. Lambrecht, J.S. Fowler, M. Sajjad, Labelled Compd. Radiopharm. 21 (1984) 1247.
[11] G.W. Kabalka, R.S. Varma, Tetrahedron 45 (1989) 6601.
[12] G.W. Kabalka, E.E. Gooch, J. Chem. Soc., Chem. Commun. (1981) 1011.
[13] G.W. Kabalka, E.E. Gooch, K.A.R. Sastry, J. Nucl. Med. 22 (1981) 908.
[14] G.W. Kabalka, M.R. Akula, J. Zhang, Nucl. Med. Biol. 29 (2002) 841.
[15] R.H. Szumigala, P.N. Devine, D.R. Gauthier, R.P. Volante, J. Org. Chem. 69 (2004) 566.
[16] A.L.S. Thompson, G.W. Kabalka, M.R. Akula, J.W. Huffman, Synthesis (2005) 547.
[17] J.M. Murphy, X. Liao, J.F. Hartwig, J. Am. Chem. Soc. 129 (2007) 15434.
[18] E. Vedejs, R.W. Chapman, S.C. Fields, L.S. Schrimpf, J. Org. Chem. 60 (1995) 3020.
[19] G.A. Molander, N. Ellis, Acc. Chem. Res. 40 (2007) 275.
[20] G.A. Molander, J. Ham, Org. Lett. 8 (2006) 2031.
[21] G.A. Molander, M. Ribagorda, J. Am. Chem. Soc. 125 (2003) 11148.
[22] G.A. Molander, R. Figueroa, J. Org. Chem. 71 (2006) 6135.
[23] G.A. Molander, J. Ham, Org. Lett. 8 (2006) 2767.
[24] G.W. Kabalka, G. Tang, A.R. Mereddy, J. Labelled Compd. Radiopharm. 50 (2007) 446.
[25] G.W. Kabalka, A.R. Mereddy, J. Labelled Compd. Radiopharm. 48 (2005) 359.
[26] G.W. Kabalka, A.R. Mereddy, H.M. Schuller, J. Labelled Compd. Radiopharm. 48 (2005) 295.
[27] G.W. Kabalka, A.R. Mereddy, Nucl. Med. Biol. 31 (2004) 935.
[28] G.W. Kabalka, A.R. Mereddy, J.F. Green, J. Labelled Compd. Radiopharm. 49 (2006) 11.
[29] H.M. Schuller, G.W. Kabalka, US Patent Appl Pub. US 2006067879, 2006.
[30] A.R. Mereddy, G.W. Kabalka, in: 16th International Symposium on Radiopharmaceutical Chemistry, Abstract 950119.
[31] A.K.L. Yuen, C.A. Hutton, Tetrahedron Lett. 46 (2005) 7899.
[32] S.J. Coutts, J. Adams, D. Krolikowski, R.J. Snow, Tetrahedron Lett. 35 (1994) 5109.
[33] M. Ganguli, V. Chandra, M.I. Kamboh, J.M. Johnston, Arch. Neurol. 57 (2000) 824.
[34] F. Yang, G.P. Lim, A.N. Befum, O.J. Ubeda, M.R. Simmons, S.S. Ambegaokar, P. Chen, R. Kayed, C.G. Galabe, S.A. Frautschy, G.M. Cole, J. Biol. Chem. 280 (2005) 5892.
[35] <http://www.clinicaltrials.gov/ct/show/NCT0009970>.
[36] E.K. Ryu, Y.S. Choe, K.-H. Lee, Y. Choi, B.-T. Kim, J. Med. Chem. 49 (2006) 6111.
[37] G. Litwinienko, K.U. Ingold, J. Org. Chem. 69 (2004) 5888.
[38] W.M. Weber, L.A. Hunsakar, S.F. Abcouwer, L.M. Deck, D.L.V. Jagt, Bioorg. Med. Chem. 13 (2005) 3811.