JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2006; **49**: 11–15.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1025

Research Article

The no-carrier-added synthesis of bromine-76 labeled alkenyl and alkynyl bromides using organotrifluoroborates

George W. Kabalka*, Arjun R. Mereddy and James F. Green
Department of Chemistry and Radiology, University of Tennessee, Knoxville, TN 37996, USA

Summary

A straightforward radiobromination procedure has been developed for the construction of radiobrominated alkenyl and alkynyl bromides. The organotrifluoroborates used as the reactive intermediates are unique in that they are quite polar and thus readily separated from the desired products. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: no-carrier-added; alkenyl bromide; alkynyl bromide; radiobromination; organotrifluoroborates

Introduction

The halogens have great potential in radiopharmaceutical design because of their ready availability and chemical reactivity. Traditionally, most radiohalogenation studies have been directed toward the insertion of radioiodine but, in recent years, there has been increased interest in radiobromination techniques due to the availability of cyclotron produced bromine isotopes and the greater stability of organic bromides when compared to organic iodides.[1–4]

We recently reported a new radioiodination procedure involving the reaction of organotrifluoroborates with sodium iodide in the presence of mild oxidizing agents.[5,6] Organotrifluoroborates have proven to be versatile intermediates in organic synthesis because of their selective chemical activity. Interestingly, they are crystalline ionic solids that are stable to both air and

*Correspondence to: George W. Kabalka, University of Tennessee, Rm. 612 Buehler Hall, Knoxville, TN 37996, USA. E-mail: kabalka@utk.edu

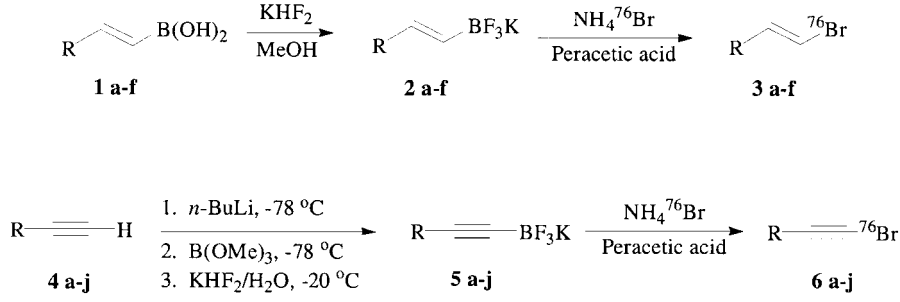
Contract/grant sponsor: The US Department of Energy; contract/grant number: DE-FG02-04ER63895
Contract/grant sponsor: Robert H. Cole Foundation
Contract/grant sponsor: NCI; contract/grant number: R24CA86307

Received 8 September 2005
Revised 17 October 2005
Accepted 19 October 2005

water for extended periods, and they are readily prepared from the corresponding boronic acids by addition of KHF_2.[7–10] Yet, trifluoroborates salts have proven to be as chemically reactive as boronic acids in organic syntheses and are far simpler to remove from reaction mixtures due to their ionic nature. We wish to report a rapid and high yield synthesis of high specific activity, bromine-76 labeled alkenyl and alkynyl bromides from the corresponding organotrifluoroborates, Scheme 1. The fact that only the products are lipophilic makes the new reaction potentially useful for a variety of Nuclear Medicine imaging applications.

Results and discussion

A number of bromine-76 labeled alkenyl and alkynyl bromides were prepared from the corresponding alkenyl- and alkynyltrifluoroborate salts. The results are summarized in Tables 1 and 2. Organotrifluoroborates **2a**−**f** and **5a**−**j** were prepared according to the literature procedure[6] and then subjected to the radiobromination procedure using no-carrier added $NH_4{}^{76}Br$ and peracetic acid in 50% aqueous THF to yield **3a**−**f** and **6a**−**j**. Bromination of alkenyl trifluoroborates **2a**−**f** was found to proceed with retention of configuration, providing ready access to a variety of (*E*) and (*Z*) alkenyl bromides. The radiochemical purity of the products typically exceed 98% and the overall radiochemical yields are good. The radiobromination of alkynyltrifluorobo-



Scheme 1. Radiobromination of alkenyl and alkynyl trifluoroborates

Table 1. Synthesis of no-carrier added bromine-76 labeled alkenyl bromines

Starting material	*R*	Product	Radiochemical yields (%)
2a	Phenyl (trans)	**3a**	70
2b	Phenyl (cis)	**3b**	69
2c	4-Methylphenyl	**3c**	74
2d	4-Chlorophenyl	**3d**	65
2e	4-Trifluoromethylphenyl	**3e**	56
2f	Heptyl	**3f**	48

Table 2. Synthesis of no-carrier added bromine-76 labeled alkynyl bromines

Starting material	*R*	Product	Radiochemical yields (%)
5a	Phenyl	**6a**	80
5b	4-Methoxyphenyl	**6b**	82
5c	4-Methylphenyl	**6c**	84
5d	4-Cyanophenyl	**6d**	78
5e	l-Cyclohexenyl	**6e**	64
5f	Hexyl	**6f**	81
5g	*t*-Butyl	**6g**	68
5h	l-Chloropropyl	**6h**	76
5i	4-*tert*-Butyldimethylsilyloxybutyl	**6i**	78
5j	4-Hydroxybutyl	**6j**	65

rates **5a**−**j** also produced radiochemical purities in excess of 98% and overall radiochemical yields >65%. It is noteworthy that these purities are, achieved (as confirmed by radio-HPLC and radio TLC) by simply passing the reaction mixture through two Sep-pak cartridges (one silica gel and one alumina cartridge). The simple isolation procedure is a consequence of the fact that the trifluoroborate starting materials are ionic and the products are lipophilic. This straightforward work up was also noted in the earlier radioiodination studies.[6]

Experimental

Radio thin layer chromatography was carried out on a Bioscan Ar-2000 imaging scanner. All boronic acids were purchased from Aldrich Chemical Company and Frontier Scientific, Inc. and used to prepare the potassium trifluoroborates.[10] The stable bromine analogues used for R_f measurements were prepared according to the literature procedure.[11] $NH_4{}^{76}Br$ was obtained from Washington University School of Medicine, St. Louis, MO, USA. The specific activity of the bromine-76 utilized was 1.09 Ci/μmole. All the reactions were carried out using dry solvents under an inert atmosphere.

Analyses of the products was performed by reversed-phase HPLC (Waters Model 510 pump and Waters 680 gradient controller) equipped with a UV detector (Waters Model 440) operating at 254 nm and a photoiodide radio detector (ORTEC Model 994). A Waters μ Bondapak C-18 (3.9 × 300 mm) was utilized with a mobile phase gradient of 35% aqueous acetonitrile at a flow rate of 1.0 ml/min. Identification of all radioactive products was confirmed by co-elution with the corresponding non radioactive bromide compound.[11] In all cases the radiochemical purity of the product was >98%. Specific activity was determined by quantitation (using experimentally determined dilution–response curves) of the UV response of a known amount of radioactivity injected onto the Waters HPLC system.

Radiosynthesis of 1-[^{76}Br]bromo-2-phenylethyne (representative procedure)

No-carrier-added $NH_4{}^{76}Br$ (140 μCi in 0.1% aqueous NH_4OH) was placed in a 2 ml Wheaton vial containing trifluoroborate **5a** (100 μl of 5.2×10^{-2} M solution in 50% aqueous tetrahydrofuran). To this was added peracetic acid (100 μl, 0.3% solution in methanol). The reaction vial was sealed, covered with aluminum foil, and the mixture stirred for 10 min at room temperature. The radiobrominated product was isolated by passing the reaction mixture through two dry Sep-pak cartridges (one silica and one alumina) to remove ionic material, using hexanes (6 ml) as eluent. The homogeneous organic eluent was analyzed using C-18 reversed phase chromatography with aqueous acetonitrile (acetonitrile: water = 65:35) as the mobile phase (flow rate = 1.0 ml/min). The retention time of **6a** was 10 min. The radiochemical yield was 80% and radiochemical purity of the l-[^{76}Br]bromo-2-phenylethyne, **6a**, was >98% (radio-HPLC and radio TLC). Recovery of the essentially pure product was achieved by removing the solvent under a stream of dry nitrogen (additional purification can be achieved by injecting this product onto the HPLC utilizing the same conditions used for radiochemical analysis). The total synthesis time was 20 min. The specific activity was determined to be 250 Ci/mmol. The alkenyltrifluoroborates were radiobrominated using a parallel procedure.

Conclusion

A convenient, high yield radiobromination procedure for preparing no-carrier-added radiobrominated alkenyl and alkynyl bromides has been developed. Because of the stability of the precursor trifluoroborates, the procedure is well suited for nuclear medicine imaging applications.

Acknowledgements

We wish to thank the US Department of Energy (DE-FG02-04ER63895) and the Robert H. Cole Foundation for Support of this research. The production of bromine-76 at the University of Washington School of Medicine is supported by the NCI grant R24CA86307.

References

1. Bolton R. Radiohalogen incorporation into organic systems. *J Label Compd Radiopharm* 2002; **45**: 485–528.
2. Katzenellenbogen JA, Senderoff SG, McElvaney KD, O'Brien HA, Welch ML. *J Nucl Med* 1981; **22**: 42–47.
3. Maziere B, Loch C. *Current Pharm Des* 2001; **7**: 1031–1943.
4. McElvany KD, Welch MJ. *J Nucl Med* 1980; **21**: 953–960.
5. Kabalka GW, Mereddy MA. *Nucl Med Biol* 2004; **31**: 935–938.
6. Kabalka GW, Mereddy MA. *J Label Compd Radiopharm* 2005; **48**: 359–362.

7. Darses S, Genet J-P, Brayer J-L, Demoute J-P. *Tetrahedron Lett* 1997; **38**: 4393–4396.
8. Molander GA, Ravero MR. *Org Lett* 2002; **4**: 107–109.
9. Kabalka GW, Venkataiah B, Dong G. *Org Lett* 2003; **5**: 3803–3805.
10. Vedejs E, Chapman RW, Fields SC, Lin S, Schrimpf MR. *J Org Chem* 1995; **60**: 3020–3027.
11. Kabalka GW, Mereddy MA. *Organometallics* 2004; **23**: 4519–4521.

