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Synthesis of novel amphiphilic pyridinylboronic acids

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Novel 3-alkoxy-2-pyridinylboronic acids bearing, in their 3-position, linear alkoxy or perfluoroalkoxy chains with *n* carbon atoms (*n* = 6, 8, 10, 12 and 18) 2a–2g are synthesized from 2-bromo-3-pyridinol, which is the common starting product. Our alternative procedure for the synthesis of 3-alkoxy-2-bromopyridine in a phase-transfer catalysis system is to carry out the reaction in a solid–liquid medium in the presence of a quaternary ammonium salt under microwave irradiation. General and versatile synthetic methods have been developed for preparation of a large variety of new 2-pyridinylboronic acids bearing two alkylated or perfluoroalkylated side chains with an ether junction in the 3-position. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: etherification; microwave; amphiphile; pyridinylboronic acids

INTRODUCTION

The pyridine ring is common to many compounds that have found applications in pharmaceuticals[1] and also in the materials sciences.[2,3] Not surprisingly, they represent a continuous challenge for the synthetic chemist.[4,5]

However, whereas there are many examples of Suzuki coupling where the pyridine motive is employed as an electrophile in the form of a halopyridine, there are many less examples where it is used as a nucleophile in the form of a pyridinylboron reagent.[6,7] There are two reasons for this: the multiple reactivity of the halopyridine in conventional methods for the synthesis of boronic acids[8,9] and the instability described for 2- and 4-pyridinylboronic acids.[10,11]

Considering the increasing use of Suzuki-type cross-coupling reaction applications,[12,13] and in order to build new pyridine libraries, we recently focused on a general method for the synthesis of heteroarylboronic acids.[9]

Our original strategy was based on the formation of a Grignard azine reagent, easily obtained by the known halogen–magnesium exchange reaction[14,15] and the particular properties of a new borylated electrophile tris(trimethylsilylborate) under mild conditions.

Access to various polyazaheterocyclic structures by application of Suzuki cross-coupling has also been developed.[16] The utility of these structures as metallic ligands in organic catalysis[17,18] led us to look for novel heteroarylboronic acids able to provide hydrophobic ligands enhancing molecular self-organization during metal-based catalysis.

With this aim in view, we report here the synthesis of alkylated (C_6–C_{18}) and perfluoroalkylated (C_{13}–C_{17}) pyridinylboronic acids **3** via 3-alkoxy-2-bromopyridines **2**.

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EXPERIMENTAL

General experimental procedure

All reactions were performed under argon and were magnetically stirred. Solvents were distilled from an appropriate drying agent prior to use: tetrahydrofuran (THF) from benzophenone–sodium, and toluene from sodium. Commercially available reagents were used without further purification unless stated otherwise. Reactions were performed under an argon atmosphere and reagents were handled with syringes through septa. NMR spectra were measured on a Bruker AC200 spectrometer (^{1}H NMR: 200 MHz; ^{13}C NMR: 50.3 MHz) and a Bruker MLS 400 spectrometer (^{1}H NMR: 400.1 MHz; ^{13}C NMR: 100.6 MHz). Microanalyses were carried out on a Perkin–Elmer 240 analyser.

General procedure for the synthesis of ethers in phase-transfer catalysis conditions under microwave irradiation in dry media

A mixture of 2-bromo-3-pyridinol (10.0 mmol), the alkylating agent (12.0 mmol), tetrabutylammonium bromide (TBAB;

0.34 g, 1.0 mmol), and a mixture of potassium carbonate (K_2CO_3; 5.6 g, 40 mmol) and potassium hydroxide (KOH; 2.2 g, 20.0 mmol) was heated in a domestic microwave oven (300 W) in an open Erlenmeyer flask for 45–60 s. After cooling, the reaction mixture was extracted with methylene chloride or ethyl acetate (3 × 530 ml). The extract was then dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to dryness. Liquid compounds were purified by distillation under reduced pressure.

General procedure for the synthesis of ethers in phase-transfer catalysis conditions under liquid–solid phase transfer in DMF

Into a 100 ml round-bottom flask with magnetic stirrer, reflux condenser and thermometer, were placed 18 mmol of 2-bromo-3-pyridinol, 1.8 mmol tetrabutylammonium bromide, 27.5 mmol of finely crushed potassium hydroxide, 23.8 mmol of alkyl bromide and dimethylformamide (15 ml). This mixture was heated to 80–130 °C for 2–6 h. After cooling, the solvent was removed under reduced pressure, and water and chloroform were added to the residue. The mixture was extracted three times with chloroform. Evaporation of the solvent gave a crude product purified by chromatography on silica gel (1/3 ethyl acetate/hexane) and repeated crystallization from *n*-hexane.

Characterization of the products 2

*3-Hexyloxy-2-bromopyridine (**2a**)*

A yellow oil was obtained in 86% yield, b.p. 102 °C (0.05 mm). Anal. Found: C, 50.88; H, 6.35; N, 5.37. Calc. for $C_{11}H_{16}BrNO$: C, 51.18; H, 6.25; N, 5.3%.

^{1}H NMR ($CDCl_3$/TMS); δ 7.8 (dd, 1H, H-6), 7.2 (dd, 1H, H-4), 7.1 (dd, 1H, H-5), 4.03 (t, 2H, –O–CH_2–), 1.85 (q, 2H, –O–C–CH_2–), 1.3 (m, 6H, –$(CH_2)_3$–), 0.9 (t, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 152.8 (C-2), 141.1 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 68.9 (O–CH_2), 33.9–22.6 (–$(CH_2)_4$), 14.1 (CH_3).

*3-Octyloxy-2-bromopyridine (**2b**)*

A yellow oil was obtained in 84% yield, b.p. 106 °C (0.05 mm). Anal. Found: C, 54.37; H, 9.87; N, 6.86. Calc. for $C_{13}H_{20}BrNO$: C, 54.56; H, 9.77; N, 6.79%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.8 (dd, 1H, H-6) 7.2 (dd, 1H, H-4), 7.1 (dd, 1H, H-5), 4.03 (t, 2H, –O–CH_2–), 1.85 (q, 2H, –O–C–CH_2–), 1.3 (m, 10H, –$(CH_2)_5$–), 0.9 (t, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 152.8 (C-2), 141.1 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 68.9 (O-CH_2), 33.9–22.6 (–$(CH_2)_6$), 14.1 (CH_3).

*3-Decyloxy-2-bromopyridine (**2c**)*

A yellow oil was obtained in 85% yield, b.p. 106 °C (0.05 mm). Anal. Found: C, 57.04; H, 7.82; N, 4.39. Calc. for $C_{15}H_{24}BrNO$: C, 57.33; H, 7.70; N, 4.46%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.8 (dd, 1H, H-6) 7.2 (dd, H-4), 7.1 (dd, H-5), 4.1 (t, 2H, –O–CH_2–), 1.70–1.90 (m, 2H, –O–C–CH_2–), 1.5 (m, 14 H, –$(CH_2)_7$–), 0.9 (t, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 152.6 (C-2), 141.5 (C-6), 137.0 (C-3), 123.3 (C-4). 119.4 (C-5), 69.3 (O–CH_2), 33.9–22.4 (–$(CH_2)_8$), 14.1 (CH_3).

*3-Dodecyloxy-2-bromopyridine (**2d**)*

A yellow oil was obtained in 82% yield, b.p. 108 °C (0.05 mm). Anal. Found: C, 59.42; H, 8.18; N, 4.15. Calc. for $C_{17}H_{28}BrNO$: C, 59.65; H, 8.24; N, 4.09%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.9 (dd, 1H, H-6) 7.3 (dd, H-4), 7.0 (dd, H-5), 4.0 (t, 2H, –O–CH_2–), 1.8 (q, 2H, –O–C–CH_2–), 1.3 (m, 18H, –$(CH_2)_9$), 0.85 (t, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 152.8 (C-2), 141.1 (C-6), 137.0 (C-3), 123.3 (C-4). 119.4 (C-5), 68.9 (O–CH_2), 33.9–22.5 (–$(CH_2)_{10}$), 14.2 (CH_3).

*3-Octadecyloxy-2-bromopyridine (**2e**)*

An amber solid was obtained in 75% yield, m.p. 68–70 °C. Anal. Found: C, 64.58; H, 9.32; N, 3.32. Calc. for $C_{23}H_{40}BrNO$: C, 64.78; H, 9.45; N, 3.28%.

^{1}H NMR ($CDCl_3$/TMS): δ 8.0 (dd, 1H, H-6) 7.19 (dd, H-4), 7.1 (dd, , 1H, H-5), 4.1 (t, 2H, –O–CH_2–), 12–1.5 (m, 32H, –$(CH_2)_{16}$–), 0.9 (t, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 152.2 (C-2), 141.8 (C-6), 137.0 (C-3), 123.3 (C-4). 119.4 (C-5), 69.3 (O–CH_2), 33.9–22.5 (–(CH2)$_{16}$), 14.2 (CH_3).

*3-(Tridecafluoro-8-decyloxy)-2-bromopyridine (**2f**)*

An amber solid was obtained in 50% yield, m.p. 120–122 °C. Anal. Found: C, 30.29; H, 1.29; N, 2.63. Calc. for $C_{13}H_7BrF_{13}NO$: C, 30.02; H, 1.36; N, 2.69%.

^{1}H NMR ($CDCl_3$/TMS): δ 8.02 (dd, 1H, H-6) 7.8 (m, 2H, H-4, H-5), 3.3 (t, 2H, –O–CH_2–), 1.7 (m, 2H, –CH_2–CF_2–). ^{13}C NMR ($CDCl_3$): δ 152.2 (C-2), 141.8 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5).

*3-(Heptadecafluoro-10-decyloxy)-2-bromopyridine (**2g**)*

An amber solid was obtained in 50% yield, m.p. 128–130 °C. Anal. Found: C, 28.80; H, 1.29; N, 2.33. Calc. for $C_{15}H_7BrF_{17}NO$: C, 29.05; H, 1.14; N, 2.26%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.8. (dd, 1H, H-6) 7.55 (m, 2H, H-4, H-5), 2.5 (t, 2H, –O–CH_2–), 1.6 (m, 2H, –CH_2–CF_2–). ^{13}C NMR ($CDCl_3$): δ 152.2 (C-2), 141.8 (C-6), 137.0 (C-3), 123.3 (C-4). 119.4 (C-5).

General procedure for the synthesis of amphiphilic pyridinylboronic acids

In a dried, argon-flushed 50 ml flask was placed ^{i}PrMgCl (1.2 mmol) and anhydrous THF 10 ml. A solution of 3-alkoxy-2-bromopyridine (1 mmol) was added at room temperature. After 2 h, the mixture was cooled to (−10 °C) and tris (trimethylsilylborate) (1.2 mmol) was added over 15 min, keeping the temperature at (−10 °C) for 2 h. A precipitate formed. The suspension was then allowed to reach room temperature slowly and stirred overnight. The resulting mixture was cooled to 0 °C and acidified to pH 6–7 by aqueous 2 M HCl, keeping the internal temperature below 5 °C. After extraction with ethyl acetate, drying and removal of solvents,

the crude acid **3**, probably containing some $B(OH)_3$, was isolated. Recrystallization from boiling MeOH followed by washing with 9/1 acetone/water gave pure boronic acid (decomposition during melting point determination).

Characterization of the products 3

*3-Hexyloxy-2-pyridinylboronic acid (**3a**)*

A white solid was obtained in 75% yield. Anal. Found: C, 59.52; H, 8.01; N, 6.01. Calc. for $C_{11}H_{18}BNO_3$: C, 59.23; H, 8.13; N, 6.28%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.8 (dd, 1H, H-6), 7.2 (dd, 1H, H-4), 7.1 (dd, 1H, H-5), 4.03 (t, 2H, $-O-CH_2-$), 1.85 (q, 2H, $-O-C-CH_2-$), 1.3 (m, 6H, $-(CH_2)_3-$), 0.9 (t, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ C-B not observed, 141.1 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 68.9 ($O-CH_2$), 33.9–22.6 ($-(CH_2)_4$), 14.1 (CH_3). ^{11}B NMR ($CDCl_3$): δ 30.

*3-Octyloxy-2-pyridinylboronic acid (**3b**)*

A white solid was obtained in 72% yield. Anal. Found: C, 62.43; H, 8.76; N, 5.46. Calc. for $C_{13}H_{22}BNO_3$: C, 62.18; H, 8.83; N, 5.58%.

^{1}H NMR ($CDCl_3$/TMS): δ 8.2 (dd, 1H, H-6), 7.3 (m, 2H, H-4, H-5), 3.93 (t, 2H, $-O-CH_2-$), 1.79 (q, 2H, $-O-C-CH_2-$), 1.29 (m, 10H, $-(CH_2)_5-$), 0.84 (t, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ C-B not observed, 141.1 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 68.9 ($O-CH_2$), 33.9–22.6 ($-(CH_2)_6$), 14.1 (CH_3). ^{11}B NMR ($CDCl_3$): δ 29.

*3-Decyloxy-2-pyridinylboronic acid (**3c**)*

A white solid was obtained in 74% yield. Anal. Found: C, 64.24, H, 9.28; N, 5.11. Calc. for $C_{15}H_{26}BNO_3$: C, 64.53; H, 9.39; N 5.02%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.8 (dd, 1H, H-6), 7.2 (dd, H-4), 7.1 (dd, H-5), 4.1 (t, 2H, $-O-CH_2-$), 1.70–1.90 (m, 2H, $-O-C-CH_2-$), 1.5 (m, 14H, $-(CH_2)_7-$), 0.9 (t, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ C–B not observed, 141.5 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 69.3 ($O-CH_2$), 33.9–22.4 ($-(CH_2)_8$), 14.1 (CH_3). ^{11}B NMR ($CDCl_3$): δ 26.

*3-Dodecyloxy-2-pyridinylboronic acid (**3d**)*

A white solid was obtained in 70% yield. Anal. Found: C, 66.78; H, 9.72; N, 4.46. Calc. for $C_{17}H_{30}BNO_3$: C, 66.46; H, 9.84; N, 4.56%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.9 (dd, 1H, H-6), 7.3 (dd, H-4), 7.0 (dd, H-5), 4.0 (t, 2H, $-O-CH_2-$), 1.8 (q, 2H, $-O-C-CH_2-$), 1.3 (m, 18H, $-(CH_2)_9-$), 0.85 (t, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ C–B not observed, 141.1 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 68.9 ($O-CH_2$), 33.9–22.5 ($-(CH_2)_{10}$), 14.2 (CH_3). ^{11}B NMR ($CDCl_3$): δ 26.

*3-Octadecyloxy-2-pyridinylboronic acid (**3e**)*

A white solid was obtained in 74% yield. Anal. Found: C, 70.26; H, 10.68; N, 3.49. Calc. for $C_{23}H_{42}BNO_3$: C, 70.58; H, 10.82; N, 3.58%.

^{1}H NMR ($CDCl_3$/TMS): δ 8.0 (dd, 1H, H-6), 7.19 (dd, H-4), 7.1 (dd, H-5), 4.1 (t, 2H, $-O-CH_2-$), 1.5 (m, 32H, $-(CH_2)_{16}-$), 0.9 (t, 3H, $-CH_3$). ^{13}C NMR ($CDCl_3$): δ C–B not observed, 141.8 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5), 69.3 ($O-CH_2$), 33.9–22.5 ($-(CH_2)_{16}$), 14.2 (CH_3). ^{11}B NMR ($CDCl_3$): δ 14.

*3-(Tridecafluoro-8-decyloxy)-2-pyridinylboronic acid (**3f**)*

A white solid was obtained in 30% yield. Anal. Found: C, 32.61; H, 1.16; N, 2.93. Calc. for $C_{13}H_7BF_{13}NO_3$: C, 32.19; H, 1.87; N, 2.89%.

^{1}H NMR ($CDCl_3$/TMS): δ 8.02 (dd, 1H, H-6) 7.8 (m, 2H, H-4, H-5), 3.3 (t, 2H, $-O-CH_2-$), 1.7 (m, 2H, $-CH_2-CF_2-$). ^{13}C NMR ($CDCl_3$): δ C–B not observed, 141.8 (C-6), 137.0 (C-3), 123.3 (C-4). ^{11_B} NMR ($CDCl_3$): δ 30.

*3-(Heptadecafluoro-10-decyloxy)-2-pyridinylboronic acid (**3g**)*

A white solid was obtained in 74% yield. Anal. Found: C, 31.10; H, 1.86; N; 2.46. Calc. for $C_{15}H_9BF_{17}NO_3$: C, 30.80; H, 1.55; N, 2.39%.

^{1}H NMR ($CDCl_3$/TMS): δ 7.8. (dd, 1H, H-6) 7.55 (m, 2H, H-4, H-5), 2.5 (t, 2H, $-O-CH_2-$), 1.6 (m, 2H, $-CH_2-CF_2-$). ^{13}C NMR ($CDCl_3$): δ C–B not observed, 141.8 (C-6), 137.0 (C-3), 123.3 (C-4), 119.4 (C-5). ^{11}B NMR ($CDCl_3$): δ 30.

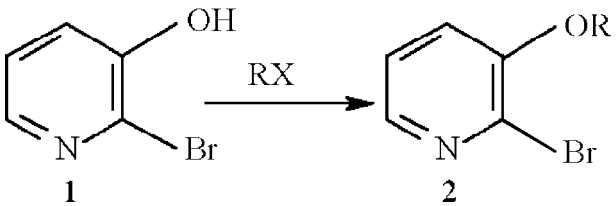
RESULTS AND DISCUSSION

Binding a long alkyl chain directly to the pyridine ring is not easy, as competitive reactions often occur.[19] Care must be taken in the choice of the base and a suitable protection of substituents may be necessary. We therefore preferred to bind the alkyl chain through an ether function from 2-bromo-3-pyridinol (**1**) as commercially available starting material, according to Scheme 1.

Synthesis of long-chain ethers from 2-bromo-3-pyridinol (1)

The direct *O*-alkylation of 2-bromo-3-pyridinol (**1**) via the standard Williamson reaction[20] leads to competitive reactions owing to the drastic experimental conditions required (basic medium, high temperatures, long reaction times).

So, the etherification of 2-bromo-3-pyridinol (**1**) was investigated by a modification of the classic Williamson synthesis by using a phase-transfer catalysis (PTC) system. Firstly, solid–liquid PTC without solvent was attempted. In these conditions, the reaction occurred by simply mixing

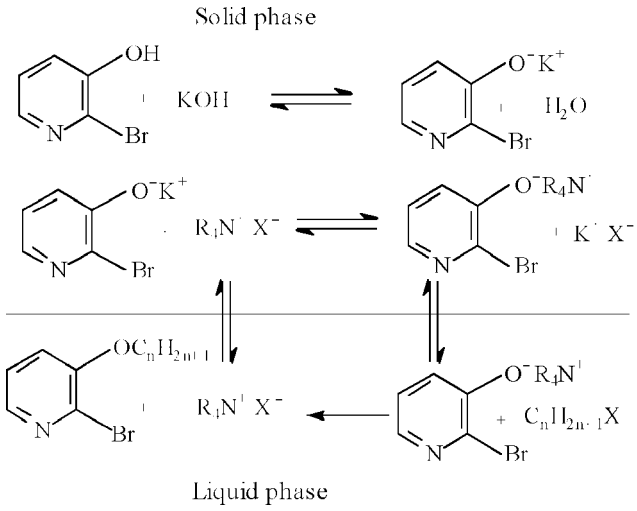


Scheme 1.

compound **1** with a 20% excess of the alkyl halide in the presence of a catalytic quantity of TBAB (10%). The reagents were adsorbed onto a mixture of K_2CO_3 and KOH, and irradiated in a beaker in a microwave oven (300 W) for various lengths of time.[21] Very short reaction times of 45 to 60 s proved sufficient to achieve *O*-alkylation almost quantitatively (Table 1). Note that attempts to perform the synthesis in the absence of catalyst (TBAB) failed. It is known that the catalytic activity of TBAB accelerates the reaction. This effect can be attributed to the formation of the tetraalkylammonium pyridinate $BrPyrO^-$, $^+NR_4$ ion pair, which is much more loosely bound and, therefore, much more reactive[22] and more soluble in the organic phase ($C_nH_{2n-1}Br$) than $BrPyrO^-$ K^+, as shown in Scheme 2, which represents this catalysis.

To our knowledge, these are the first examples of the alkylation of the bromopyridinate ion under irradiation in the absence of solvent.

However, the use of this process is not possible for the solid C_{17} alkylating agents and for all the perfluorinated derivatives. From these compounds, *O*-alkylation was achieved by using the organic solvent dimethylformamide. A temperature of 80 to 130 °C and reaction times of 2 to 6 h were then necessary to synthesize the pyridine ethers in good yield (Table 1). These experimental conditions, applied to liquid alkylating agents (C_6 to C_{12} compounds), led to good yields of *O*-alkylated products, but stressed the usefulness of the protocol using microwave irradiation (much shorter reaction times).



Scheme 2.

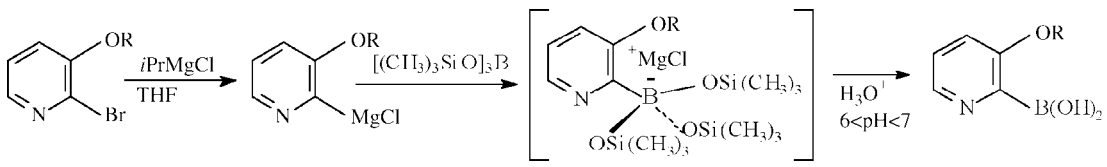
Synthesis of long-chain pyridinylboronic acids (3)

We investigated the potential offered by the transmetallation reaction between pyridylmagnesium chloride and trimethylsilylborate that we recently reported[9] (Scheme 3). The amphiphilic pyridinylboronic acids synthesized are given in Table 2. The presence of the long chain does not disturb the halogen–magnesium exchange, thus allowing the transmetallation to occur in good conditions. It is necessary to hydrolyse the intermediate 'ate borate complex' at a slightly acidic pH ($6 < pH < 7$) to avoid the formation of by-products, which

Table 1. Reaction of 2-bromo-3-pyridinol with alkyl and perfluoroalkyl halides

		PTC solid–liquid				
		Microwave irradiation		Dimethylformamide		
RX	Product	Time (s)	Yield (%)[a]	Time (h)	Temperature (°C)	Yield (%)[a]
$CH_3(CH_2)_5Br$	**2a**	45	86	2	80	82
$CH_3(CH_2)_7Br$	**2b**	50	84	2	80	81
$CH_3(CH_2)_9Br$	**2c**	60	85	2	80	83
$CH_3(CH_2)_{11}Br$	**2d**	60	82	2	82	82
$CH_3(CH_2)_{17}Br$	**2e**	—	—	6	130	75
$CF_3(CF_2)_5CH_2CH_2I$	**2f**	—	—	6	130	50
$CF_3(CF_2)_7CH_2CH_2I$	**2g**	—	—	6	130	50

[a] Isolated product.



Scheme 3.

Table 2. Synthesis of 3-alkoxy-2-pyridinylboronic acids (**3**)

R	Product	Yield (%)[a]	^{11}B NMR δ (ppm)
$CH_3(CH_2)_5-$	**3a**	75	30
$CH_3(CH_2)_7-$	**3b**	72	29
$CH_3(CH_2)_9-$	**3c**	74	26
$CH_3(CH_2)_{11}-$	**3d**	70	26
$CH_3(CH_2)_{17}-$	**3e**	62	14
$CF_3(CF_2)_5CH_2CH_2-$	**3f**	60	30
$CF_3(CF_2)_7CH_2CH_2-$	**3g**	62	30

[a] Isolated product.

complicate the extraction and purification of the pyridinylboronic acids **3.** The perfluorinated chain is involved in the various steps of exchange or transmetallation. The relatively low yields of the pure isolated products are mainly due to the difficulties met in extraction and purification. This aspect remains to be optimized.

CONCLUSIONS

We have improved the Williamson method of synthesis of bromopyridinyl ethers, by working in conditions of solid–liquid PTC without solvent or in the presence of dimethylformamide. These conditions allow C_6 to C_{18} alkyl chains and C_{13} and C_{17} perfluorinated chains to be grafted onto 2-bromo-3-pyridinol with excellent yields. In addition, these ethers, submitted to a process of bromine–magnesium exchange followed by transmetallation with trimethylsilylborate, lead to the synthesis of new amphiphilic pyridinylboronic acids. The use of these compounds for the synthesis of new metallic ligands is in progress.

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