Journal of Fluorine Chemistry 130 (2009) 806–809

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Ipso-amidation of arylboronic acids: Xenon difluoride-nitriles as efficient reagent systems☆

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ARTICLE INFO

Article history:
Received 15 April 2009
Received in revised form 14 May 2009
Accepted 18 May 2009
Available online 27 May 2009

Keywords:
Xenon difluoride
Nitriles
Anilide synthesis
Radical cation reaction
Amidation

ABSTRACT

The xenon difluoride-mediated, *ipso*-amidation of boronic acids has been achieved for the first time under mild conditions. This method provides a simple, one-pot procedure for the direct synthesis of a series of anilides from the corresponding arylboronic acids and alkyl/aryl nitriles. Arylboronic acids bearing electron donating groups gave anilides in high yields, while moderate yields were observed for those bearing electron withdrawing groups. A plausible mechanism involving the formation of an aryl radical cation through single electron transfer by xenon difluoride, followed by the nucleophilic addition of the nitrile, is proposed.

1. Introduction

The preparation of amides by various methods has been well documented in the literature. Ritter et al. reported the direct preparation of amides from nitriles and secondary/tertiary alcohols [1,2] or olefins [3,4] in strong acid medium [5–7]. Since the feasibility of the reaction is dependent on the stability of the carbocation formed from the alcohol or olefin during the reaction, application of this method for general practical purposes is limited, although in our laboratory such reactions have been successfully employed in preparing amides and trifluoromethylated amides in good yields [8,9]. This reaction does not proceed with primary alcohols, substituted phenols (to give anilides), or unsubstituted olefins. More recently, Chan et al. have coupled arylboronic acids with amides in the presence of copper(II) acetate to form anilides [10], and the method has been further improved by Xie and co-workers [11]. However, both methods require preformed amide, reducing the synthetic utility of the reaction. Anilides are important precursors for many dyes, drugs and pharmaceuticals. For example, acetanilide, also known as Antifebrin, has been widely used in analgesic and antipyretic drugs [12,13].

Xenon difluoride, XeF_2, has proven to be a versatile electrophilic fluorinating agent in organic synthesis [14,15], and has been effective for the desilylative *ipso*-fluorination of trimethyl(phenyl)silane to yield fluorobenzene [16]. It is also known to be a powerful oxidizing agent [15,17,18]. So far, no XeF_2-mediated amidation reactions have been reported. Herein, we report the facile preparation of anilide derivatives from the reaction of arylboronic acids with alkyl/aryl nitriles in the presence of XeF_2.

2. Results and discussion

As a part of our attempt to expand the utility of XeF_2 for *ipso*-fluorination of substrates other than phenylsilanes, the reaction of XeF_2 with phenylboronic acid was carried out in acetonitrile. Complete conversion of the starting materials was observed in a short period of time (30 min for a 1 mmol scale reaction). Analysis of the product obtained after the work-up of the reaction mixture showed that *ipso*-amidation occurred at the boronic acid functionality. The main product separated was acetanilide. In order to ascertain that *ipso*-amidation occurred predominantly, the reaction was repeated in an excess of benzonitrile. As expected, benzanilide was separated as the major product. The general application of this method has been investigated by conducting this reaction with various substituted phenylboronic acids in acetonitrile (Scheme 1). Reaction of the parent phenylboronic acid with propiononitrile as well as benzonitrile yielded the corresponding anilides in good yields. *Ipso*-amidation reactions were found to be feasible in most of the cases, albeit with varying yields.

The reactions were found to occur under mild reaction conditions (0 °C to room temperature), and required short reaction times (0.5–2.5 h). In these reactions the nitrile is used as both the

☆ Dedicated to Prof. Henry Selig on the occasion of receiving the 2009 American Chemical Society Award for Creative Work in Fluorine Chemistry.

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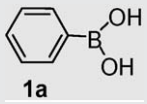
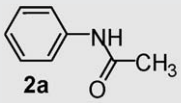
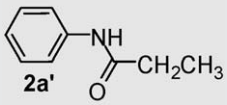
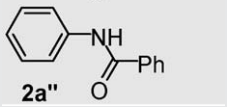
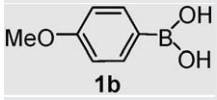
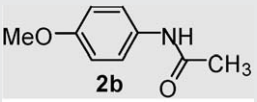
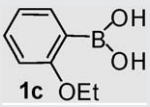
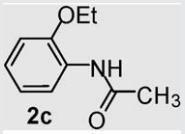
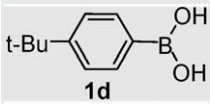
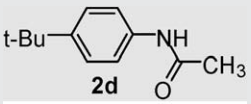
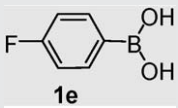
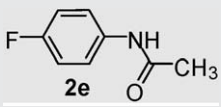
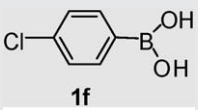
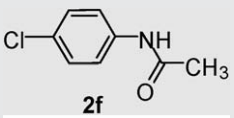
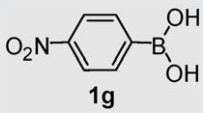
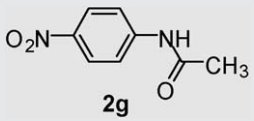
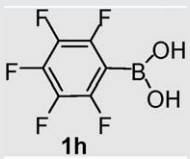
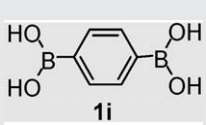
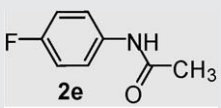
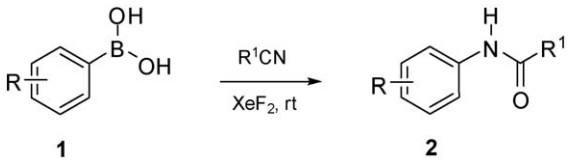
doi:10.1016/j.jfluchem.2009.05.015

reagent and the solvent, and no strong acid was required. These features make this method very convenient and useful. The only by-products of the reaction were xenon gas (evolved during the reaction), the tetrafluoroborate anion (identified by its ^{19}F NMR chemical shift δ, −147.97 ppm, and characteristic secondary boron-10 isotope shift of 0.669 ppm) as well as minor amounts of $B(OH)_nF_{3-n}$ species and HF (all formed by successive fluorination of the cleaved boronic acid functionality); the latter species was neutralized with sodium bicarbonate solution, and all by-products were removed by extraction. The source of characteristic orange-

Table 1
Reactions of arylboronic acids with XeF_2 in nitrile solution.

Arylboronic acid (**1a–i**)	Nitrile	Time (h)	Anilide (**2a–e**)	Yield (%)
 **1a**	CH_3CN	0.5	 **2a**	84
	CH_3CH_2CN	0.5	 **2a'**	58
	PhCN	0.5	 **2a''**	70
 **1b**	CH_3CN	1.0	 **2b**	95
 **1c**	CH_3CN	1.5	 **2c**	33
 **1d**	CH_3CN	1.5	 **2d**	58
 **1e**	CH_3CN	2.5	 **2e**	40
 **1f**	CH_3CN	1.5	 **2f**	41
 **1g**	CH_3CN	2.0	 **2g**	13
 **1h**	CH_3CN	1.0	No identifiable products	
	C_6F_5CN	2.0	No reaction	
 **1i**	CH_3CN	1.5	 **2e**	43



Scheme 1. Xenon difluoride-mediaited *ipso*-amidation of arylboronic acid.

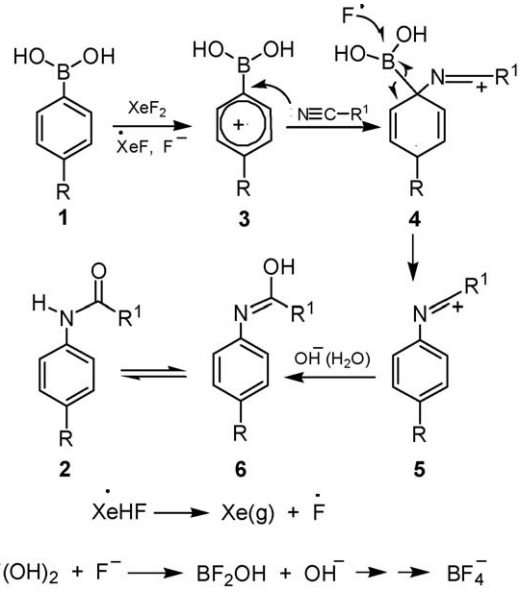
brown color of the reaction mixture (which was retained on the column during column chromatography) is presumably due to the oligomerization of aromatic rings by a radical cation-induced chain reaction (*vide infra*). Table 1 shows the scope of the reaction and the yields of the products.

The synthetic role of xenon difluoride in this reaction was determined by performing similar reactions of phenylboronic acid in the presence of other chemical oxidants such as pyridinium chlorochromate (PCC), cerium ammonium nitrate (CAN), manganese dioxide (MnO_2), potassium permanganate ($KMnO_4$), and sodium periodate ($NaIO_4$). A blank reaction was also conducted in the absence of XeF_2 and other oxidants in an excess of acetonitrile at elevated temperatures. In all of these cases no *ipso*-amidation, and hence no anilide formation, was observed.

The chemical yields of the XeF_2-mediated *ipso*-amidation products were also found to vary with the electronic nature of the aromatic substituent in arylboronic acids. The presence of an electron donating group (EDG; i.e., OMe) increased the yield relative to phenylboronic acid, while the presence of an electron withdrawing group (EWG) decreased the yield. In order to prepare perfluorobenzanilide, perfluorophenylboronic acid was treated with perfluorobenzonitrile under similar conditions. No reaction was observed due to extremely low reactivity of the substrates. It was interesting to note the behavior of 2-ethoxyphenylboronic acid and 2,4,6-trimethylphenylboronic acid, both electron rich substrates, towards this reaction; 2-ethoxyphenylboronic acid gave 2-ethoxyacetanilide with only 33% isolated yield, while no reaction was observed in the case of 2,4,6-trimethylphenylboronic acid. In both cases the steric effect appears to predominate over the electronic effect because of the possible significant hindrance by the *ortho* substituent during *ipso*-substitution. This phenomenon has also been observed by Xie and co-workers in their copper(II) acetate-mediated *N*-arylation reactions [11]. The reactivity observed for various substituted arylboronic acids shown in Table 1 is in agreement with a mechanism involving the formation of a radical cation, as proposed by Lotian and Ramsden, for the reaction of XeF_2 with $PhSiMe_3$ [16]. A plausible mechanism is shown in Scheme 2. From the proposed mechanism the complete dominance of *ipso*-amidation over *ipso*-fluorination is evident, as CH_3CN is known to be a better nucleophile than F^-, and is in much higher concentration in the reaction mixture. Similar reactions carried out between phenylboronic acid and XeF_2 in C_6F_6 and CH_2Cl_2 failed to give the corresponding fluoroarene.

Failure to achieve similar reactivity with the cyclic, phenylboronic acid 1,3-propanediol ester and with potassium trifluorophenylborate indicates that the OH groups on boron are crucial for the reaction for the conversion of **5** to the enol **6**, which tautomerizes to the anilide **2**. Further studies with other electrophilic sources of fluorine, such as Selectfluor and *N*-fluorobenzenesulfonimide (NFSI), showed no reaction, even at 80 °C, suggesting that generation of a radical cation intermediate such as **3** is a key step in the anilide formation.

It is interesting to note that the reaction of 1,4-phenylenediboronic acid with XeF_2 in CH_3CN failed to yield the bis-*ipso*-amidated product, but instead gave 4-fluoroacetanilide in moderate yield (43%, last entry in Table 1). The analogous reaction, however, between 4-acetamidobenzeneboronic acid and XeF_2 failed to yield any isolable products. These results suggest that *ipso*-fluorination occurs prior to *ipso*-amidation, but the reasons for *ipso*-fluorination in this case remain unclear.



Scheme 2. Mechanism of *ipso*-amidation of arylboronic acid using the XeF_2–nitrile system.

3. Conclusions

Direct preparation of anilides by *ipso*-amidation of arylboronic acids from the corresponding alkyl and arylnitriles has been achieved for the first time using xenon difluoride. Failure of other various oxidants in the *ipso*-amidation of arylboronic acids using nitriles clearly demonstrates the potential of the XeF_2–nitrile system for *ipso*-amidation. Observation of partial *ipso*-fluorination in 1,4-phenylenediboronic acid unveils a probable XeF_2-mediated *ipso*-fluorination strategy for the conversion of arylboronic acids to the corresponding fluoroarenes.

4. Experimental

4.1. General

Acetonitrile (DriSolv, >99.8%, EMD Chemicals Inc.), benzonitrile (99%, Aldrich) and pentafluorobenzonitrile (99%, Aldrich) were used as received. Xenon difluoride (>99.5%, Synquest Laboratories Inc.) was stored in the glove box and used as received. Phenylboronic acid, 4-nitrophenylboronic acid (both from Alfa Aesar), 4-fluorophenylboronic acid, 1,4-phenylenebisboronic acid, pentafluorophenylboronic acid, 4-methoxyphenylboronic acid, 2-ethoxyphenylboronic acid (all from Aldrich), *t*-butyl-phenylboronic acid, and 2,4,6-trimethylphenylboronic acid (both from Oakwood Products) were used as received. Proton, ^{13}C, and ^{19}F NMR were spectra were recorded on a Varian AS 400 Inova NMR spectrometer. Proton and ^{13}C NMR chemical shifts were determined relative to the ^1H and ^{13}C chemical shifts of the solvent, $CDCl_3$ (residual proton resonance, δ 7.26 ppm for ^1H and δ 77.16 ppm for ^{13}C). Fluorine-19 chemical shifts were referenced to that of $CFCl_3$ added in the solvent ($CDCl_3$). GC/MS data were acquired on a Hewlett Packard 5890 Series II Gas Chromatograph coupled with 5971 Series Mass Selective Detector. All products were identified by comparing their spectra with those of the authentic samples.

4.2. Typical ipso-amidation procedure for the direct preparation of anilides from arylboronic acids

CAUTION! *Combining solid arylboronic acids with XeF_2 leads to spontaneous combustion, even in an inert (argon) atmosphere. Only solutions of the two reagents should be combined.*

A 50-mL round bottom flask, fitted with a gas inlet tube (with Teflon stopcock), was equipped with a magnetic stirrer (Teflon) and a rubber septum. A small, positive flow of argon was maintained through the gas inlet by means of a tygon tube connection through a Schlenk line. The arylboronic acid (1 mmol) was then weighed into the flask. Inside the drybox, xenon difluoride (1.5 mmol, 3 mmol in the case of 1,4-phenylenediboronic acid) was weighed into a tapered round bottom flask fitted with a rubber septum. In the fumehood, nitrile was syringed under argon into the flask containing the arylboronic acid (3 mL) and into the flask with the XeF_2 (4 mL). The XeF_2–nitrile mixture was then sonicated until the XeF_2 had fully dissolved, and was then syringed into the mixture of partially dissolved arylboronic acid–nitrile mixture at 0 °C. The reaction mixture was stirred for 0.5–2.5 h depending on the boronic acid substrate taken. As the reaction proceeded, the solution became homogenous and orange-brown in color.

The resulting mixture was extracted with CH_2Cl_2 (3× 10 mL), washed with 10% $NaHCO_3$ solution (10 mL) and water (2× 10 mL) followed by brine (10 mL), and dried over sodium sulfate. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography (60–200 mesh silica, hexane/ethyl acetate as the eluent). The products were identified by spectral analysis (^{1}H, ^{13}C, ^{19}F NMR, and GC/MS) and the structures were confirmed by comparing their spectral data with those of the authentic samples. Purity was found to exceed 95% for all compounds as determined by GC/MS.

4.3. Spectral data of products

4.3.1. Acetanilide (2a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (bs, 1H, N–H), 7.48 (m, 2H), 7.30 (m, 2H), 7.09 (m, 1H), 2.18 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 168.42, 137.98, 129.13, 124.46, 119.98, 24.63. GC/MS (*m*/*z*): 135 (M^+, 26), 92 (M^+-COCH_3, 100).

4.3.2. Propionanilide (2a′)

^{1}H NMR ($CDCl_3$): 7.51 (m, 2H), 7.31 (m, 2H), 7.16 (bs, 1H, N–H), 7.10 (m, 1H), 2.39 (q, 2H, CH_2), 1.25 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 172.08, 163.72, 138.07, 129.13, 124.30, 119.85, 30.92, 9.81. GC/MS (*m*/*z*): 149 (M^+, 3), 92 ($M^+-1-COCH_2CH_3$, 100).

4.3.3. Benzanilide (2a″)

^{1}H NMR ($CDCl_3$): 7.87 (m, 2H), 7.81 (bs, 1H, N–H), 7.65 (m, 2H), 7.55 (m, 1H), 7.48 (m, 2H), 7.37 (m, 2H), 7.16 (m, 1H). ^{13}C NMR ($CDCl_3$): 165.88, 138.02, 135.10, 131.96, 129.21, 128.91, 127.13, 124.70, 120.32. GC/MS (*m*/*z*): 196 (M^+-1, 36), 104 ($M^+-1-NHC_6H_5$, 100).

4.3.4. 4-Methoxyacetanilide (2b)

^{1}H NMR ($CDCl_3$): 7.38 (m, 2H), 7.17 (bs, 1H, N–H), 6.85 (m, 2H), 3.78 (s, 3H, OCH_3), 2.15 (s, 3H, $COCH_3$). ^{13}C NMR ($CDCl_3$): 168.32, 156.59, 131.02, 122.05, 114.26, 55.6, 24.50. GC/MS (*m*/*z*): 164 (M^+-1, 24), 122 (M^+-COCH_3, 44), 107 (M^+-COCH_3 & CH_3, 100).

4.3.5. 2-Ethoxyacetanilide (2c)

^{1}H NMR ($CDCl_3$): 8.38 (m, 1H), 7.78 (bs, 1H, N–H), 7.00 (m, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 4.10 (q, 2H, OCH_2CH_3), 2.18 (s, 3H, $COCH_3$), 1.45 (t, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$): 168.25, 147.00, 127.85, 123.55, 121.04, 119.83, 110.87, 64.21, 25.09, 14.97. GC/MS (*m*/*z*): 179 (M^+, 32), 136 (M^+-COCH_3, 33), 103 (M^++1$-COCH_3$ & CH_2CH_3, 100).

4.3.6. 4-t-Butylacetanilide (2d)

^{1}H NMR ($CDCl_3$): 7.41 (m, 2H), 7.37 (m, 2H), 7.18 (bs, 1H, N–H), 2.16 (s, 3H, CH_3), 1.30 (s, 9H, t-butyl). ^{13}C NMR ($CDCl_3$): 168.21, 147.31, 135.18, 125.82, 119.77, 34.36, 31.34, 24.54. GC/MS (*m*/*z*): 191 (M^+, 27), 134 ($M^+-C(CH_3)_3$, 100), 91 ($M^+-C(CH_3)_3$ & $COCH_3$, 21).

4.3.7. 4-Fluoroacetanilide (2e)

^{1}H NMR ($CDCl_3$): 7.44 (m, 2H), 7.40 (bs, 1H, N–H), 6.99 (m, 2H), 2.16 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 168.50, 159.49 (d, $^1J_{C-F}$, 243 Hz), 133.95 (d, $^4J_{C-F}$, 3.0 Hz), 121.92 (d, $^3J_{C-F}$, 7.5 Hz), 115.73 (d, $^2J_{C-F}$, 23.2 Hz), 24.52). ^{19}F NMR (376 MHz, $CDCl_3$): −118.03 (m). GC/MS (*m*/*z*): 152 (M^+-1, 17), 110 (M^+-COCH_3, 100).

4.3.8. 4-Chloroacetanilide (2f)

^{1}H NMR ($CDCl_3$): 7.44 (m, 2H), 7.27 (m, 2H), 7.20 (bs, 1H, N–H), 2.17 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 168.38, 136.50, 129.42, 129.15, 121.16, 24.73. GC/MS (*m*/*z*): 169 (M^+, 18), 127 (100), 126 (M^+-COCH_3, 98).

4.3.9. 4-Nitroacetanilide (2g)

^{1}H NMR ($CDCl_3$): 10.33 (bs, 1H, N–H), 8.76 (m, 2H), 8.21 (m, 2H), 2.15 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 169.25, 136.14, 125.87, 123.40, 122.33, 20.12. GC/MS (*m*/*z*): 180 (M^+, 18), 137 (M^+-COCH_3, 100), 91 (M^+-COCH_3 & NO_2, 46).

Acknowledgment

Financial support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

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