Pergamon

Tetrahedron Letters 42 (2001) 4083–4085

TETRAHEDRON
LETTERS

α-(Trifluoromethyl)ethenyl boronic acid as a useful trifluoromethyl containing building block. Preparation and palladium-catalysed coupling with aryl halides

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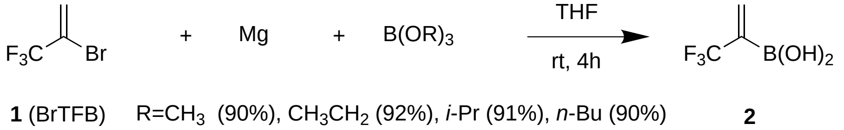
Received 12 January 2001; accepted 12 April 2001

Abstract—α-(Trifluoromethyl)ethenyl boronic acid was conveniently prepared from the reaction of readily available 2-bromotrifluoropropene with alkyl borate and magnesium in one-pot. This boronic acid can undergo palladium-catalysed coupling reactions with aryl halides to afford a series of useful α-(trifluoromethyl)styrene derivatives in high yield. © 2001 Elsevier Science Ltd. All rights reserved.

In recent years, trifluoromethylated organic molecules have been drawing much attention due to their unique biological properties[1] and considerable effort has been paid to the development of new synthetic routes to these fluorinated compounds.[2] Alkyl alkenyl borates are synthetically useful intermediates, which undergo a wide variety of reactions to afford many different types of organic compound.[3] Direct hydroboration of alkynes or reactions of alkenyl metallic compounds with alkyl borates are well documented for the preparation of alkenyl boronic acids.[4] To the best of our knowledge, no example has been reported of the preparation of a vinyl boronic acid bearing an α-trifluoromethyl group, because α-trifluoromethyl vinyl metal compounds undergo extremely facile defluorination. The defluorination of an α-CF_3-attached carbanion is assisted by a countercation which has a strong affinity for the fluorine atom. Therefore, it could be anticipated that use of a countercation with a weak affinity for fluorine would impede the defluorination process. On this basis, we have successfully prepared a trifluoromethylethenyl zinc reagent which is stabilised by TMEDA.[5] Although the zinc reagent was stable and underwent cross coupling reactions under inert atmosphere, its sensitivity to air and moisture limited the scope of its reactions. In our ongoing program, we sought to prepare a (trifluoromethyl)ethenyl agent which could be stable and easy to handle. Herein we would like to describe a successful preparation of an α-(trifluoromethyl)ethenyl boronic acid from readily available 2-bromotrifluoropropene, an alkyl borate and magnesium in a one-pot process and its reaction with aryl halides catalysed by palladium.

2-Bromotrifluoropropene (**1**, BrTFP), which could be easily obtained by dehydrobromination of the dibromo adduct of trifluoropropene,[6] reacted with magnesium to give a complex mixture of products. However, we found that mixtures of an alkyl borate (1.5 equiv.), magnesium (1.2 equiv.) and BrTFP **1** (1.2 equiv.) in THF on stirring at room temperature for several hours gave high yields of α-(trifluoromethyl)ethenyl boronic acid **2** after acidic work up (Scheme 1). Compound **2** displayed a singlet in its ^{19}F NMR at δ_{TFA} −12.0 ppm



Scheme 1.

Keywords: α-(trifluoromethyl)ethenyl boronic acid; Suzuki cross-coupling reaction.

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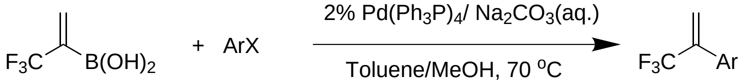
PII: S0040-4039(01)00636-0

(s, upfield positive) and was very stable for several months even if in the presence of air and moisture.[7]

With the α-(trifluoromethyl)ethenyl boronic acid **2** in hand, we undertook a study of its reactivity. Suzuki cross couplings of alkenyl boronic acids with electrophiles in the presence of a catalytic amount of palladium have been shown to be efficient for the formation of carbon–carbon bonds.[8] Encouraged by the easy preparation and the remarkable stability of the α-(trifluoromethyl)ethenyl boronic acid **2**, we were interested in the feasibility of using this reagent for cross-coupling reactions with electrophiles catalysed by transition metals. We found that α-(trifluoromethyl)ethenyl boronic acid **2** was able to undergo Suzuki cross coupling reactions with various aryl halides promoted by palladium to afford the α-trifluoromethyl styrene derivatives in high yield (Scheme 2).

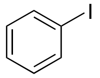
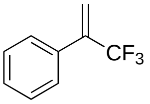
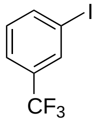
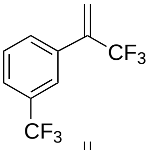
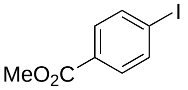
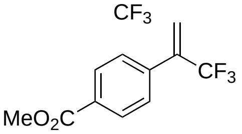
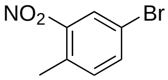
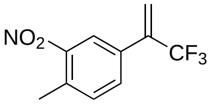
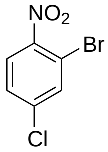
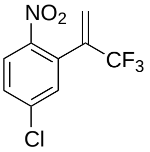
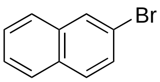
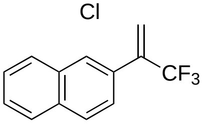
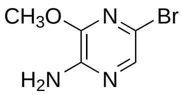
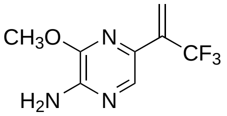
The experimental results are summarised in Table 1. With aryl iodides, the cross-coupling reaction proceeded smoothly and was complete in less than 6 h with the products being obtained in excellent yields (entries 1–3). The coupling reaction with α-(trifluoro-



2 **3** **4**

Scheme 2.

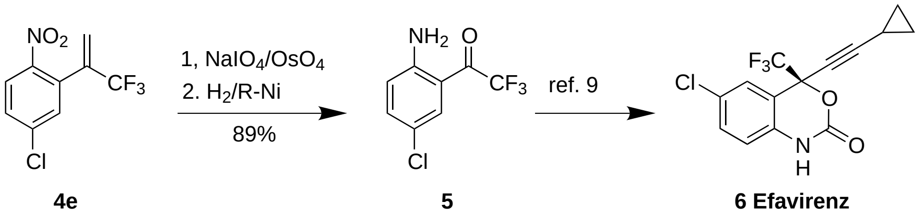
Table 1. Suzuki cross-coupling of boronic acid **2** with aryl halides **3**

Entry[a]	ArX(**3**)	React. Time	Product(**4**)[b]	Yield(%)[c]
1	 **3a**	6	 **4a**	95
2	 **3b**	4	 **4b**	96
3	 **3c**	5	 **4c**	90
4	 **3d**	12	 **4d**	78
5	 **3e**	12	 **4e**	81
6	 **3f**	8	 **4f**	98
7	 **3g**	8	 **4g**	96

[a] All reactions were carried out under a nitrogen atmosphere using an aryl halide (1 mmol), boronic acid **2** (1.2 mmol), sodium carbonate (1mL of 1.0 M aqueous solution), $Pd(PPh_3)_4$ (2% mol) in toluene-methanol (10 ml, 5:1) at 70 °C.

[b] All new compounds were fully characterised by IR, NMR, MS and elemental analysis.

[c] Isolated yield based on aryl halide.



Scheme 3.

methyl)ethenyl boronic acid **2** could be extended to aryl bromides bearing strong electron withdrawing groups in the aryl ring (entries 4–5). In addition, 2-naphthyl bromide **3f** and 2-amino-3-methoxy-5-bromopyrazine **3g** (entries 6–7) also underwent the palladium-catalysed coupling reaction with α-(trifluoromethyl)ethenyl boronic acid **2** to give the coupling products in excellent yields.

It is known that the trifluoroketone **5** is an important intermediate for the preparation of efavirenz,[9] which is a potent nonnucleosidal HIV reverse transcriptase inhibitor approved by the FDA for the treatment of AIDS.[10] The trifluoroketone **5** has been synthesised from the reaction between *n*-butyllithium and an *N*-protected aniline with ethyl trifluoroacetate at low temperature. This process suffers from high cost and strict reaction conditions.[11] The α-trifluoromethylstyene **4e** was easily converted into ketone **5** in high yield simply by oxidation of the ethenyl bond using $NaIO_4$ and catalytic OsO_4 (0.01 equiv.) in *tert*-$BuOH/H_2O$ (4:1), followed by hydrogenation over Raney Ni in ethanol (Scheme 3).

In summary, the α-(trifluoromethyl)ethenyl boronic acid **2** was conveniently prepared from 2-bromotrifluoropropene, an alkyl borate and magnesium in a one-pot process. The palladium-catalysed cross coupling of this boronic acid with aryl halides provides an efficient method for the preparation of α-trifluoromethylstyrene derivatives under mild conditions. The stability and tolerance to air and moisture of this reagent allow easy storage and manipulation. The synthetic utility of the α-(trifluoromethyl)ethenyl boronic acid in Suzuki cross coupling reactions has revealed the potential of this reagent as a new versatile trifluoromethyl containing building block for the synthesis of bioactive trifluoromethylated organic compounds.

References

1. Filler, R.; Kobayashi, Y.; Yagupoyashi, L. M. *Organofluororine Compounds in Medicinal Chemistry and Biomedical Application*; Elservier Science: Amsterdam, 1993.
2. (a) *New Fluorinating Agents in Organic Synthesis*; German, L; Zemskov, S., Eds.; Springer-Verlag: Berlin, Heidelberg, 1989; (b) *Synthetic Fluorine Chemistry*; Olan, G. A.; Surya Prakash; Chambers, R. D., Eds.; John Wiley & Son: New York, 1992.
3. (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463; (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
4. *The Borance, Carborance, and Carbocation Continum*; Casanova, J., Ed.; John Wiley & Son: New York, 1998.
5. (a) Jiang, B.; Xu, Y. Y. *J. Org. Chem.* **1991**, *56*, 7336; (b) Jiang, B.; Xu, Y. Y. *Tetrahedron Lett.* **1992**, *33*, 511.
6. Henne, A. L.; Nager, M. *J. Am. Chem. Soc.* **1951**, *73*, 1042.
7. The procedure for preparation of boronic acid **2**: A mixture of BrTFP (1.75 g, 10 mmol), magnesium (0.29 g, 12 mmol) and trimethyl borate (3.12 g, 30 mmol) in anhydrous THF (20 mL) stirred at rt for 4 h. Then, 6 M HCl (50 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined extract was washed with brine and evaporated to give **2** (126 mg, 90%), which was enough pure to be used for Suzuki cross coupling reaction. ^{19}F NMR δ_{TFA}: −12.0 (s, 3F) ppm; ^{1}H NMR($CDCl_3$) δ: 6.72 (s, 2H) ppm; MS(EI) *m*/*z*: 140 (M^+), 121 (M^+−F), 70 (M^+−1−CF_3).
8. (a) Watanebe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
9. (a) Thompson, A.; Corley, E. C.; Huntington, M. F.; Crabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028; (b) Tan, L.; Chen, C. Y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 711.
10. Young, S. D.; Britcher, S. F.; Tan, L.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I. W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602.
11. (a) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590; (b) Thompson, A. S.; Corely, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 8937.