Pergamon

Tetrahedron Letters, Vol. 38, No. 38, pp. 6781-6784, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01552-9

Studies on the Synthesis, Characterisation and Reactivity of Aromatic Diboronic Acids

Matthew H. Todd, Shankar Balasubramanian, and Chris Abell*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK

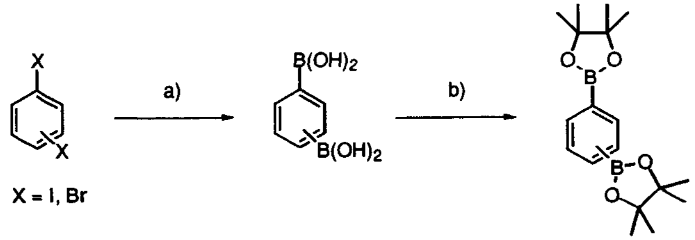
Abstract: The synthesis and characterisation of 1,3- and 1,4-phenyl diboronic acids are described, and the palladium-catalysed couplings between 1,4-phenyl diboronic acid and a number of aryl iodides is reported. © 1997 Elsevier Science Ltd.

In this paper we report on the synthesis and characterisation of diboronic acids, and their reaction with aryl iodides to make terphenyls by the Suzuki reaction.[1] Terphenyls are of interest in the area of liquid crystals,[2] but have not previously been synthesised in this way. Diboronic acids have been used in the study of sugar complexes,[3] but otherwise have not been studied extensively, possibly due to difficulties involved in their analysis (see below). The potential usefulness of the Suzuki reaction in coupling aromatic dihalides in the preparation of polymers[4] and dendrimers[5] has been reported.

Synthesis

The synthesis of diboronic acids from aryl dihalides has been reported.[6] We have fine-tuned this procedure and additionally exploited the facile formation of pinacol esters of boronic acids[7] to form the diesters of the diboronic acids (Scheme 1). The diesters can then be purified by flash chormatography giving an alternative route to purification other than differential crystallisation of the diacid away from the monoacid.

Scheme 1. Preparation of Diboronic Acids and Esters.



Reagents and conditions : a) i) 3 eq. n-BuLi (dropwise addition), Et_2O, -78 °C, then warm to r.t., stir 1 h, then cool to -78 °C; ii) 4 eq. $B(O^iPr)_3$, -78 °C then warm to r.t. and stir for 2-3 h; iii) 1M aq. HCl r.t., 1 h. 50-60 % overall yield. b) 2.4 eq. pinacol, MeOH, $MgSO_4$, r.t. 16 h.

Treatment of 1,3-dibromobenzene with butyl lithium at -78 °C for 2 minutes results in only monolithiation, such that addition of trimethylborate gave 3-bromophenylboronic acid in 55% recrystallised yield. If the lithiation reaction is allowed to warm to room temperature and stirred for 1 hour before being recooled to -78 °C, significant amounts of dilithiated species are formed, from which the diboronic acid can be generated in 50-60% yield. The conversion of the diacid to the pinacol diester proceeded very smoothly to give pure diester with no purification other than a standard aqueous workup (to which the diester was stable).

Characterisation

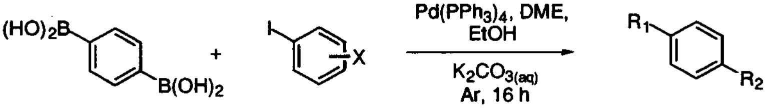
Boronic acids in general present a host of difficulties with regard to analysis (and therefore preparation). The principal difficulty is their spontaneous condensation to boroxines to varying degrees. These difficulties are compounded in the case of diboronic acids, where discrete anydrous forms may not be predicted.

FT-IR spectra of diboronic acids heated to constant mass at 100 °C usually reveal a complex set of peaks for OH stretching, and a cluster of peaks due to aromatic stretches. The strong O-B signal at 1310-1380 cm^{-1} is usually visible, but not as clearly as for monoboronic acids. Microanalysis and melting points are of little use, and EI- and MALDI-MS have failed to show any recognisable ions (EI-MS is an excellent method of seeing the boroxine peak of monoboronic acids). TLC is not useful due to the acids' polarity and their faintness under UV irradiation and using a number of common stains.

NMR spectroscopy has proved the most instructive method of characterisation. Whilst we have not found that solvents influence the spectra of either mono- or diboronic acids,[8] we have been able to improve the quality of the spectra greatly by addition of a small quantity of DCl. Thus the ^{1}H NMR spectrum of 1,4-benzene diboronic acid in MeOD gave two very broad peaks at 7.56 and 7.68 ppm, which were transformed into a sharp singlet at 7.68 ppm upon addition of a single drop of DCl. The ^{13}C NMR spectrum was similarly improved. The carbon attached to boron is often not seen in the ^{13}C NMR spectrum. ^{11}B NMR spectroscopy has also been a useful technique, and shows a broad peak at 28 ppm for 1,4-benzenediboronic acid ($BF_3.OEt_2$ reference as 0 ppm).

Reactivity

The use of diboronic acids to make terphenyls by a double Suzuki coupling has been studied with a range of aryl iodides under standard Suzuki coupling conditions (Scheme 2 and Table 1).[9] The reactions with iodobenzene, iodo 3-bromobenzene, iodo 4-nitrobenzene and iodo 3-fluorobenzene proceeded smoothly, to give mixtures of di- and mono-substituted products (the hydroxy group arises from the standard oxidative work-up of unreacted boronic acid).[9] The higher yields of terphenyls obtained from reactions with electron deficient aryl iodides is in line with similar observations for the Suzuki coupling of monoboronic acids.[1] In comparison, coupling with 4-iodoanisole proceeded in low yield and gave a mixture of additional products. These presumably arise through a palladium-phosphine aryl exchange between the palladium catalyst and the phosphine ligands,[10] as has previously been observed in the monoboronic Suzuki[11] and Stille[12] reactions. In this reaction, 41% of the phosphine phenyl substituents were isolated in the products shown.



Scheme 2. Diboronic Acid Coupling Reaction.[9]

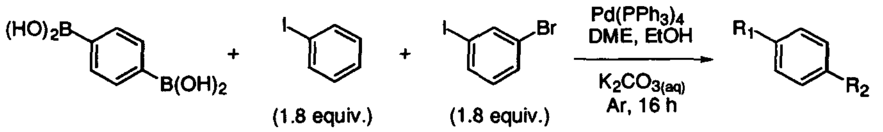
When some of the above reactions were repeated with a separate but spectroscopically identical (by NMR and IR) commercial batch of diboronic acid (which was noticably less soluble in DME/EtOH/water), surprisingly poor results were obtained. Couplings gave lower yields of expected products (e.g. 11% for the iodo 3-fluorobenzene experiment) and higher yields of unwanted halide homo-coupled products.[13] In order to try to overcome these problems, the coupling reaction was tried on the pinacol diboronic ester with fluoro 3-iodobenzene, but gave lower overall yields (24% product based on moles of diboronic acid used) and higher yields of unwanted products (such as homocoupling of the boronic acids themselves[14]), possibly arising from the increased steric crowding around the boron center and the resultant difficulty in activating the boron centre with base.

Table 1. Synthesis of Symmetrical Terphenyls from 1,4-Benzene Diboronic Acid and Aryl Iodides.

X	R_1	R_2	Yield (%)[a]
H	Ph	Ph	38
	Ph	OH	11
3-Br	3-BrPh	3-BrPh	65
	3-BrPh	OH	6
4-NO_2	4-NO_2Ph	4-NO_2Ph	66
	4-NO_2Ph	OH	20
3-F	3-FPh	3-FPh	59
	3-FPh	OH	18
4-MeO	4-MeOPh	4-MeOPh	13
	4-MeOPh	Ph	10
	Ph	Ph	11
	4-MeOPh	MeO	3
	4-MeOPh	H	4
	Ph	H	3
	4-MeOPh	OH	9
	Ph	OH	16

[a] Yields based on moles of diboronic acid used.

The chemistry was explored further with a view to exploiting the differential reactivity of the aryl iodides to make unsymmetrical terphenyls. A competition experiment was performed reacting 1.8 equivalents each of two aryl iodides with one equivalent of diboronic acid (Scheme 3 and Table 2).



Scheme 3. Competitive Diboronic Acid Coupling Reaction with Two Aryl Iodides.

Table 2. Products Formed in Competition Experiment with Iodobenzene and 3-Bromoiodobenzene.

R_1	R_2	Yield (%)[a]
3-BrPh	3-BrPh	17
3-BrPh	OH	13
3-BrPh	Ph	33
Ph	OH	8
Ph	Ph	3

[a] Yields based on moles of diboronic acid used.

The surprising outcome of this experiment is that the major product is the mixed terphenyl. The higher yields of products dervived from 3-bromoiodobenzene was expected, but the selectivity observed was unexpectedly low. Another important observation is that despite the presence of an excess of aryl iodides some boronic acid still did not couple. It appears that under the conditions of the Suzuki reaction there is some undefined decomposition of the boronic acids over time.

In a second attempt to form mixed terphenyls, a sequential reaction was carried out by reacting 1,4 phenyl diboronic acid, with 0.9 equivalents of iodobenzene, followed 2 hours later by 0.9 equivalents of iodo 3-bromobenzene. The unsymmetrical terphenyl was only isolated in 6% yield, the symmetrical terphenyl (15%) and the phenol (33%) derived from monocoupling of iodobenzene were major products, with very little of the corresponding products from 3-bromoiodobenzene being isolated (0.2% and 3% respectively). The low overall yield of products from this reaction is in part due to the shorter reaction times (2 h instead of 16 h). It is also probable that the diboronic acid, present in excess for the first part of the reaction, polymerised on heating.[14]

These studies have shown that diboronic acids can be used to make symmetrical terphenyls in good yield. However the attempts to form unsymmetrical terphenyls proved less successful, primarily because differently substituted aryl iodides did not show sufficiently differential reactivity.

Acknowledgement. We thank Zeneca Pharmaceuticals for a studentship (to MHT). SB is a Royal Society University Research Fellow

REFERENCES AND NOTES

1. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
2. Hird, M.; Gray, G. W.; Toyne, K. J. *Mol. Cryst. Liq. Cryst.* **1991**, *206*, 187-204; Andersch, J.; Tschierske, C. *Liquid Cryst.* **1996**, *21*, 51-63; Andersch, J.; Diele, S.; Lose, D.; Tschierske, C. *Liquid Cryst.* **1996**, *21*, 103-113; Hird, M.; Toyne, K. J.; Gray, G. W. *Liquid Cryst.* **1993**, *14*, 741-761; Hird, M.; Toyne, K. J. *J. Mater. Chem.* **1995**, *5*, 2239-2245; Hird, M.; Toyne, K. J.; Gray, G. W.; McDonnell, D. G.; Sage, I. C. *Liquid Cryst.* **1995**, *18*, 1-11.
3. Takeuchi, M.; Mizuno, T.; Shinmori, H.; Nakashima, M.; Shinkai, S. *Tetrahedron* **1996**, *52*, 1195-1204; James, T. D.; Shinmori, H.; Shinkai, S. *Chem. Commun.* **1997**, 71-72; Deng, G.; James, T. D.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 4567-4572; Uggla, R.; Sundberg, M. R.; Nevalainen, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1741-1748.
4. Tour, J. M.; Lamba, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 4935-4936; Goldfinger, M. B.; Swager, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 7895-7896; Hu, Q.-S.; Vitharana, D.; Liu, G.-Y.; Jain, V.; Wagaman, M. W.; Zhang, L.; Lee, T. R.; Pu, L. *Macromolecules* **1996**, *29*, 1082-1084; Hodge, P.; Power, G. A.; Rabjohns, M. A. *Chem. Commun.* **1997**, 73-74; Galda, P.; Rehahn, M. *Synthesis* **1996**, 614-620.
5. Miller, T. M.; Neenan, T. X.; Zayas, R.; Bair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018-1025.
6. Clement, R.; Champetier, G. *C. R. Acad. Sc. Paris (C)* **1966**, 1398-1400; Musgrave, O. C. *Chem. & Ind.* **1957**, 1152; Nielsen, D. R.; McEwan, W. E. *J. Am. Chem. Soc.* **1957**, *79*, 3081-3084; Coutts, I. G. C.; Goldschmid, H. R.; Musgrave, O. C. *J. Chem. Soc. C.* **1970**, 488-493.
7. Waas, J. R.; Sidduri, A.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 3717-3720.
8. Hensel, V.; Schlüter, A.-D. *Liebigs Ann./Recueil* **1997**, 303-309.
9. Typical reaction procedure : To DME (4 ml) in the dark and under argon were added 1, 4-benzene diboronic acid (100 mg, 0.60 mmol), aryl iodide (1.8 eq.), tetrakis (triphenylphosphine) palladium (0) (approx. 5 mol% w.r.t. iodide) and 2 M K_2CO_3 solution (2 eq.). The reaction mixture was heated at 80 °C for 16 h, before being allowed to cool to r.t., and was then stirred with 30% H_2O_2 (0.1 ml) for 1 h. 1 N HCl (5 ml) and diethyl ether (5 ml) were added, the layers were filtered through celite and washed through with further ether and HCl. The aqueous phase was extracted with ether (2 x 5 ml), then the combined organic layers were washed with saturated $NaHCO_3$ solution (5 ml), brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The products were purified by flash column chromatography (silica gel, from hexane:DCM to DCM:MeOH) and dried under high vacuum. ^1H, ^{13}C NMR spectra, and EI- or FAB-MS were obtained for all samples. Some of the terphenyl products, particularly the dinitro p-terphenyl, are not very soluble in many common organic solvents.
10. Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313-6315.
11. O'Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679-6680.
12. Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12-13.
13. Amatore, C.; Carré, E.; Jutand, A.; Tanaka, H.; Ren, Q.; Torii, S. *Chem. Eur. J.* **1996**, *2*, 957-966.
14. Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346-2351.

(*Received in UK* 21 *July* 1997; *accepted* 25 *July* 1997)