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BORINIC ACIDS: NOVEL INTERMEDIATES IN REGIOSPECIFIC SYNTHESIS OF BIARYLS

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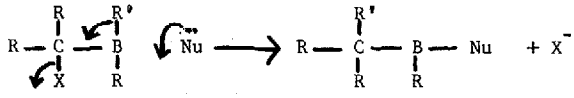
Borinic acids, unlike organoboranes[2,3], organoborate anions[4], and, to a lesser extent, boronic acids[2,3,5], have been seldom used as intermediates in synthetic organic chemistry. Borinic acids, however, are readily accessible compounds which can be isolated, characterised and stored as ethanolamine esters (boroxazolidines)[6,7,8,9]. Following a study of the reaction of borinic acids with electrophiles, we wish to report that they are useful intermediates in the synthesis of biaryls.

Depending upon reaction conditions, it might be expected that 2-aminoethyl dithien-2-yl borinate, I, would react with, for example, bromine, in three ways:

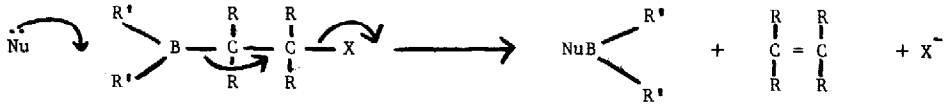
i) To give 2-bromothiophene. Arylboron compounds are very susceptible to electrophilic attack by halogens at the ipso position[10] with subsequent cleavage of the C-B bond[11]. This attack is promoted by electron-donating groups: thus, relative rates for C-B bond cleavage in substituted boronic acids include p-MeO, 1.45×10^6; p-Me, 79; H, 1.0 and p-COOEt, 0.01[11,12].

ii) To give 2-aminoethyl (5-bromo-2-thienyl)-2-thienylborinate. Thiophene-3-boronic acid, for example, reacted with either bromine in chloroform or with N-bromosuccinimide in carbon tetrachloride to give 5-bromothiophene-3-boronic acid[13].

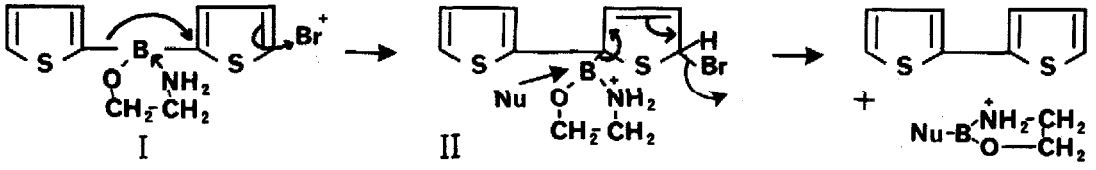
iii) To give 2,2'-bithienyl. α-Haloalkylboranes[14] and α-haloalkyl borinic acids[15] undergo a facile rearrangement under the influence of base with transfer of alkyl group from boron to carbon:



Electrophilic attack at the 5-position of the borinic acid, I, might therefore initiate a similar rearrangement to give II. Now it is known that β-hetero derivatives of organoboranes readily undergo either spontaneous or base-promoted elimination to form olefins[2,4]:



We reasoned that II would undergo an equally facile vinylogous β-elimination to give 2,2'-bithienyl, and that this might be developed into a general synthesis of biaryls.



I II

When I was treated with a variety of brominating agents (phenyl-trimethylammonium tribromide in chloroform; N-bromosuccimide in chloroform/acetic acid; dioxan dibromide in tetrahydrofuran or chloroform; bromine in carbon tetrachloride/pyridine; bromine in methanol; bromine in acetic acid) the mixture of products contained variable amounts of 2,2'-bithienyl and 5,5'-dibromo-2,2'-bithienyl. 2-Bromothiophene and 2,5-dibromothiophene were also produced but none of the bromoderivative of the borinic acid was detected. Bromine and N-bromosuccinimide were selected as the reagents during the further study of the effect of changing various reaction parameters on the yield of 2,2'-bithienyl.

Dialkyl borinic acids are susceptible to radical bromination[15]. 2-Aminoethyl dithien-2-yl borinate, I, was therefore treated with N-bromosuccinimide/azobisisobutyronitrile in refluxing carbon tetrachloride in the hope that a radical-induced rearrangement might be achieved without the undesirable C-B bond cleavage; 2-bromothiophene and 2,5-dibromothiophene were the only products. 2,2'-Bithienyl was most efficiently prepared from I by the following procedure: N-bromosuccinimide (1.0 mol. equiv.) was added (either portionwise as a solid or in solution in dichloromethane) during ca. 10 minutes to the borinate, I, (1.0 mol. equiv.) at 0-5° in dichloromethane/aqueous buffer, pH9 (DMSO was an acceptable co-solvent). Ten minutes after completing the addition, the organic layer was separated, washed free of base, and evaporated to dryness. The 2,2'-bithienyl was isolated either by dry-column chromatography or by distillation under reduced pressure. The results of representative reactions using the same procedure are summarized below:

Starting material	Biaryl produced[a]	(% yield)[b]
2-aminoethyl dithien-2-yl borinate	2,2'-bithienyl	50
2-aminoethyl 2-furyl-2-thienyl borinate	2-(2-thienyl)furan	20[c]
2-aminoethyl phenyl-2-thienyl borinate	2-phenylthiophene	58
2-aminoethyl phenyl-3-thienyl borinate	3-phenylthiophene	43
2-aminoethyl-4-biphenylyl-2-thienyl borinate	2-(4-biphenylyl)thiophene	40
2-aminoethyl(4-methyl-2-thienyl)-2-thienyl borinate	4-methyl-2,2'-bithienyl	46

a. All the products exhibited spectra in accordance with the assigned structures.

b. Isolated yield.

c. 5-bromo-2-(2-thienyl)furan was obtained in 50% yield when 2 mol. equiv. of NBS was used.

Although the above examples confirm that borinic acids are potentially useful intermediates in the synthesis of biaryls, the outcome is dependent upon the susceptibility of the borinic acid to electrophilic attack, and, as the examples below indicate, is, therefore, critically influenced by the directive effects and the orientation of the substituents within the starting material. Thus, 2-aminoethyl bis (5-methyl-2-thienyl) borinate under conditions found optimal for coupling, gave only 2-bromo-5-methylthiophene; and 2-aminoethyl (5-methyl-2-thienyl)-2-thienyl borinate, although giving some of the desired 5-methyl-2,2'-bithienyl (ca. 3%), also gave 2-bromo-5-methylthiophene as the major product. Furthermore, 2-aminoethyl diphenyl borinate did not give biphenyl (bromobenzene and 2,4,6-tribromophenol were the only products), and neither 2-aminoethyl(2-methoxyphenyl)phenyl borinate nor 2-aminoethyl(4-methoxyphenyl)phenyl borinate gave any of the desired methoxybiphenyl. 2-Aminoethyl(3-methoxyphenyl)phenyl borinate, however, gave some 3-methoxybiphenyl (< 1%).

Thus, for a successful biaryl synthesis the electrophilic substitution at the ipso position leading to C-B bond cleavage must be less favourable than the alternative attack leading to a transition state in which the carbon bearing the boron is formally electron deficient. The desired reaction is promoted by electron donating substituents meta- to the boron. It is also probable that the undesirable ipso attack might be limited by i) electron attracting groups ortho- to boron; ii) bulky electrophiles - although iodine, surprisingly, gave exclusive C-B bond cleavage; iii) bulky substituents on boron.

From the practical standpoint the method is attractive because of its mildness, cleanliness, and the ease with which the biaryl may be isolated from the more volatile haloarenes. The main virtue of the method, however, lies in its excellent regioselectivity: the new C-C bond is formed exclusively between the C atoms originally bound to boron. No crossed products were detected from unsymmetrical borinic acids.

The preliminary data presented suggests that the borinic acid route complements the existing methods for biaryl synthesis and we are hopeful that it will find useful application. Further work aimed at a more precise definition of the scope and limitations of the method is in hand. Attention will be focused on limiting the C-B bond cleavage and on a study of other

electrophiles.

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