Pergamon

Tetrahedron Letters 40 (1999) 3895–3898

TETRAHEDRON LETTERS

Arbuzov Reaction of 1-Iodoboronates as a Means of Preparing C1-Bridged Phosphonoboronates

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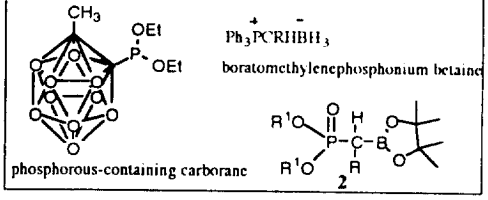
Received 20 January 1999; accepted 15 March 1999

Abstract: The Arbuzov reaction of 1-iodoalkylboronates and $P(OMe)_3$ proceeds smoothly to give phosphonoboronates **2**, in good yields. Essentially no alkene formation is observed, apparently because of prior complexation of the phosphite with boron as observed by ^{11}B NMR. Selective hydrolysis of the methyl esters is possible by treatment of **2** with excess Me_3SiBr followed by methanol to give **3**. Treatment of **3** with 6N HCl leads to the free phosphonoboronic, **4a**.

Keywords: Arbuzov reactions, boron and compounds, phosphorous acids and derivatives.

The P-C-B fragment represents a class of compounds whose potential has not been fully explored. By and large two types of compounds incorporating the P-C-B fragment have been reported. Carboranes containing both tri- and pentavalent phosphorous,[1] and boratomethylenephosphonium betaines (Fig. 1).[2] The latter have been prepared by reaction of phosphorous ylides with halogen boranes[3] or boron hydrides[4] while the former derive from lithiated carboranes and tri- and pentavalent halophosphorous[5] compounds. The potential applications of carborane-containing organophosphorous compounds include boron neutron capture therapy.[6] They also possess various biological activities and have been evaluated as pesticides, gametocides and bactericides.[7] While these two classes of compounds are intriguing in their own right, their high costs of manufacture almost preclude their use. On the other hand, the potential for biomedical and other applications incorporating the P-C-B fragment in a molecule, and the possibly rich chemistry to be expected from the juxtaposition of two heteroatoms with different chemical reactivity, prompted us to investigate the synthesis, chemistry and biological activity of C1 bridged phosphonoboronates, **2**, not previously described in the literature. Chemically, although the mean bond enthalpy of Me_3B is considerably greater than that of Me_3P and the electronegativity of B and P are comparable,[8] the empty 2p orbital on boron should render the B-C bond more reactive than the P-C bond. From a medicinal chemistry standpoint, compounds **2** may be viewed as the boron analogs of bisphosphonates.[9] The use of both boronates and phosphonates as analog inhibitors of enzymes is well known.[10] Boronic acids are exceptionally potent inhibitors of serine proteases.

Fig. 1. Compounds with P-C-B fragment



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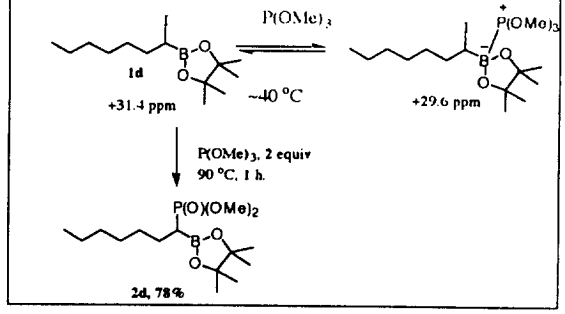
PII: S0040-4039(99)00563-8

Because their potency as inhibitors of serine proteases is widely believed to derive from the boronyl groups's ability to mimic the transition state of the enzyme-catalyzed reaction,[11] boronic acid inhibitors are of considerable interest to drug development. Cytotoxicity of boron anlogues has been reported.[12] The use of bisphosphonates in the treatment of bone neoplasms is well documented.[13] However, with the exception of olpadronate which is soluble in water, bisphosphonates have poor solubility and may easily precipitate in the digestive media.[14] Replacing a phosphonato group of the bisphosphonates with a boronato group would give a molecule of lower polarity and thus possibly increased solubility in digestive media. In addition, synergism between the two groups may lead to compounds of increased effectiveness as inhibitors through a new mechanism of action. Similar reasoning can be applied to the potential use of **2** as analogs of bisphophonates in the treatment of osteoroporosis.[15] Alternatively, **2** can be viewed as analogs of phosphonoacetic acid and therefore may possess various antiviral activity associated with the former.[16] Preparation of phosphonates by the Arbuzov reaction is well documented.[17] However, the Arbuzov reaction with a secondary or tertiary alkyl halide generally does not lead to the desired products either, giving alkenes instead, or does not take place at all.[18] Presumably the alkenes are formed by an elimination reaction with the phosphite acting as the base. Nucleophilic attack on boranes containing leaving groups on the α-carbon are known to proceed by prior coordination of the nucleophile with boron, followed by migration of the nucleophile to the carbon bearing the leaving group.[19] Thus it was reasonable to assume that the Arbuzov reaction with a 1-haloalkylboronate would also proceed with formation of an "ate" complex. Indeed, when **1d** (+ 31.4 ppm) was mixed with $P(OMe)_3$ in $CDCl_3$ and heated to ~40 °C, a new peak appeared in the ^{11}B NMR at +29.6 ppm, in addition to the peak of the starting material. The reaction appears to be an equilibrium (Scheme 1).

Scheme 1. Reactions of $P(OMe)_3$ with 1d.



On a preparative scale, **1d** and $P(OMe)_3$ (2 equiv) were mixed neat and heated to 90 °C for an hour. Analysis by GCMS indicated that **2d** was obtained as the only product in 78% isolated yield (Scheme 1).[20] Alkene formation was not observed. Results with various **1** are listed in Table 1. Phosphonoboronates, **2**, are oils, stable to air and water. The iodides for this study were prepared from the corresponding borazirconocenes.[21] The order of reactivity of the alkyl halide in the Arbuzov reaction is known to be, I>Br>Cl. We also observed this trend. The bromine analog of **1d** bromide was investigated and the desired reaction was observed. The corresponding chloride

Table 1. Arbuzov reaction of 1-iodoalkylboronates 1 with $P(OMe)_3$[a]

	R	%Arbuzov Product[b]	% Elimination Product[b]	% Isolated Yield
a	H	100	0	87
b	n-C_3H_7	100	0	65
c	n-C_5H_{11}	93	0	75
d	n-C_6H_{13}	84	0	78
e	n-$Cl(CH_2)_4$	80	5	55
f	$PhCH_2$	63	0	28
g	$(CH_3)_3C$	2[c]	13[c]	d

[a] Reaction conditions: **1** (1 mmol), $P(OMe)_3$ (2 mmol), 90 °C, 1 h. [b] Of total reaction mixture. [c] A complex mixture of products was obtained. [d] The product could not be isolated.

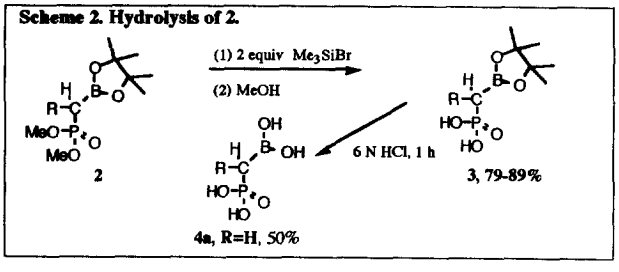
Table 2. Arbuzov reaction of 1-iodoalkylboronates, 1, with various phosphites[a]

R	$P(OMe)_3$ %[b] 2, (% alkene)	$P(OEt)_3$ %2, (% alkene)	$P(O\text{-}iPr)_3$ %2, (% alkene)	$P(OBu)_3$ %2, (% alkene)
C_6H_{13}	83, (0)	100, (0)	41, (0)	42, (0)
$Cl(CH_2)_4$	80, (5)	98, (0.5)	98, (0.5)	98, (0.5)
$(CH_3)_3C$	2, (13)	8, (5)	N.R	N.R

[a] In the cases of Et, I-Pr and Bu, one equiv of phosphite was used. In the case of Me, two equiv were used. [b] All percentages are in terms of the total reaction mixture as determined by GCMS

was completely unreactive. The results in Table 1 are noteworthy in that for the first time we have demonstrated that the Arbuzov reaction with secondary alkyl halides is general, albeit with the help of boron. Remarkably, even for **entry f** (Table 1), (R=$PhCH_2$), no alkene formation was observed. All this indicates that formation of the "ate" complex is preferred to proton abstraction by $P(OMe)_3$. The reaction of different phosphites structure and representative compounds **1** was also investigated (Table 2). Except for non-reactive **1g** (R=t-Bu), selectivity of the phosphites were comparable, though the yields varied. In the end we selected $P(OMe)_3$ as the phosphite of choice due to the facile hydrolysis of the methyl phosphonates. Since it is the free acids that are usually responsible for biological activity of both phosphonates and boronates, we investigated hydrolysis of **2.** Complete hydrolysis of **2** with refluxing 6N HCl to the free acid was not effective. Mixtures of partially removed methyl groups and/or the pinacol group were obtained. More vigorous conditions, i.e., 12 N HCl (reflux, 1h), resulted in the decomposition of **2.** However, a two step procedure for the selective hydrolysis of the methyl groups was successful. Treatment of **2** with 5 equiv of Me_3SiBr (1h, 25 °C) followed by addition of by methanol and immediate evaporation of volatiles cleanly led to **3** (Scheme 2).[22] Yields were uniformly high. Subsequent hydrolysis of **3** with 6N HCl (reflux, 1h) furnished **4** (Scheme 2) in 50% yield. In conclusion, we have described a new class of compound, **2**, and reported some initial chemical studies. Additional chemical and biological studies are underway and will be subject of future communications.

Scheme 2. Hydrolysis of 2.



Acknowledgment Our thanks for financial support of this project goes to the Israeli Science Foundation Grant 186/98-12.0 and the Hebrew University. Thanks also to the Wolfson Foundation for the purchase of a Hewlet-Packard GCD GCMS.

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(20)**Preparation of 2d:** Trimethylphosphite (180 mg, 1.44 mmol) was added in one portion to freshly prepared **1d** (500 mg, 0.72 mmol) and the reaction mixture was heated with a stirring for 1h at 90^{0}C. Then the reaction mixture was cooled to room temperature and chromatographed on Silica gel (10% MeOH in CH_2Cl_2) to yield **2d** as a coloreless oil. (78 % yield). ^{1}H NMR ($CDCl_3$): δ= 0.82 (t, 3H), 1.23 (m,1H),1.23 (s,12H), 1.24-1.25 (m, 8H),1.65 (m,2H), 3.68 (s, 3H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$): δ= 13.83, 22.25, 24.60, 24.83, 24.91, 29.96, 30.19, 31.41, 52.33; ^{31}P NMR ($CDCl_3$): δ = 33.70; ^{11}B NMR ($CDCl_3$): δ = 32.31.

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