

5-ISOXAZOLEBORONIC ACIDS

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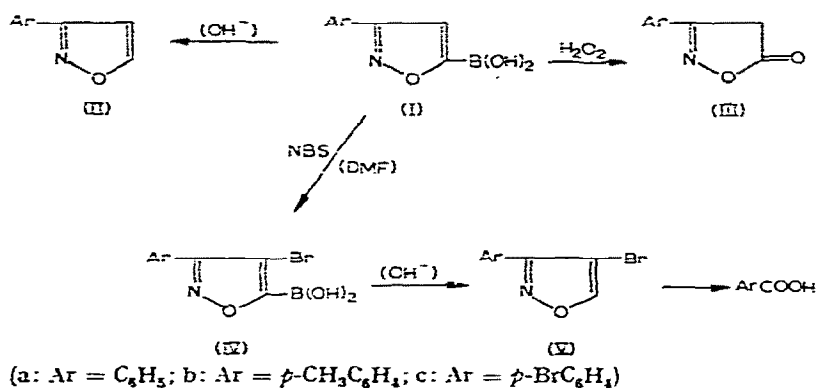
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Heterocyclic boronic acids have not been studied very extensively. Among the five-membered nitrogen-containing ring derivatives, the 5-carbomethoxy- and 4,5-diphenyl-3-pyrazoleboronic acids¹ have to be mentioned: they have been obtained by 1,3-dipolar cycloaddition of ethyl diazoacetate and diphenyldiazomethane, respectively, to dibutyl ethynylboronate.

We now report the preparation of some 3-aryl-5-isoxazoleboronic acids and their derivatives. The most general method of preparation of the boronic acids, that starting from arylmagnesium halides, did not seem promising for the isoxazole nucleus, since 5-haloisoxazoles failed to give Grignard reagents². In view of the well-known structural analogy between diazoalkanes and nitrile oxides³⁻⁵, we studied the cycloaddition of nitrile oxides with dibutyl ethynylboronate.

From the reaction between benzonitrile oxide and dibutyl ethynylboronate in ether good yields of 3-phenyl-5-isoxazoleboronic acid (Ia) were obtained: its structure was assigned on following evidence (see Chart I): (a) the IR-spectrum shows a broad band at 3.0μ (-OH) and the UV-spectrum shows a $\lambda_{max} = 242 \text{ m}\mu$ ($\log \epsilon 4.14$), a value very similar to that of 3-phenylisoxazole⁶; (b) the product was deboronated easily to 3-phenylisoxazole by alkaline hydrolysis; (c) the oxidative deboronation yielded 3-phenyl-5-isoxazolone, thus confirming the 5-position of the boronic group. The cycloaddition involves therefore the same orientation as in the case of propiolic acid³.



The initially formed dibutyl ester could not be isolated.

The isoxazoleboronic acid reacts with diethanolamine to yield a stable ester and with *o*-aminophenol or *o*-phenylenediamine to give the corresponding 2-substituted

1,3,2-benzoxazaboroline or 1,3,2-benzodiazaboroline, respectively, whereas tentative halogenation with I_2/KI or bromine does not give satisfactory results. Bromination was effected by reaction with *N*-bromosuccinimide in *N,N*-dimethylformamide at room temperature. Under those conditions good yields of the somewhat unstable 3-phenyl-4-bromo-5-isoxazoleboronic acid (IVa) were obtained. The structure assigned is supported by the most easy deboronation to 3-phenyl-4-bromoisoxazole (Va), already known and easily oxidizable to benzoic acid.

The synthesis has been extended to other examples: starting from *p*-tolu- or *p*-bromobenzonitrile oxides the corresponding 3-aryl-5-isoxazoleboronic acids (Ib) and (Ic) respectively, have been obtained. Their structures were assigned on the basis of the reactions summarized in Chart I.

Nitrile oxides add therefore, as in the case of propiolic acid, to the β -carbon atom of dibutyl ethynylboronate.

EXPERIMENTAL

All m.p.'s are uncorrected. UV spectra were determined in 95% EtOH by means of a Perkin-Elmer model 137 UV spectrophotometer. Microanalyses were performed by Dr. LUCIA MAGGI DACREMA.

3-Phenyl-5-isoxazoleboronic acid (Ia)

An ethereal solution of benzonitrile oxide (obtained as under ref. 4 from 5.5 g of benzohydroxamyl chloride) was added to a solution of dibutyl ethynylboronate⁷ (5.4 g) in absolute ether. The mixture was refluxed for 4 h. The solvent was removed to leave a thick oil, in which thin-layer chromatography revealed the presence of notable amounts of the isoxazoleboronate, which could not be isolated. After exposure to air overnight the oil had completely solidified, yielding white crystals (4.0 g), m.p. 115–121°. These were recrystallized from aq. methanol or chloroform to give colourless needles, m.p. 123–124° dec. (Found: C, 57.56; H, 4.12; N, 7.64. $C_9H_5BNO_3$ calcd.: C, 57.19; H, 4.27; N, 7.41%.)

Esterification of (Ia) with diethanolamine in ether afforded the diethanolamine ester, which was recrystallized from acetone to give white crystals, m.p. 191°. (Found: C, 60.39; H, 6.08; N, 11.00. $C_{13}H_{15}BN_2O_2$ calcd.: C, 60.50; H, 5.85; N, 10.86).

On refluxing (Ia) with *o*-aminophenol in toluene, 2-(3-phenyl-5-isoxazolyl)-1,3,2-benzoxazaboroline, m.p. 160–162° (from toluene) was obtained. (Found: C, 68.34; H, 4.25; N, 10.50. $C_{15}H_{11}BN_2O_3$ calcd.: C, 68.74; H, 4.23; N, 10.69%.)

Upon refluxing (Ia) with *o*-phenyldiamine in toluene, 2-(3-phenyl-5-isoxazolyl)-1,3,2-benzodiazaboroline, m.p. 230–231° dec. (from toluene), was obtained. (Found: C, 69.18; H, 4.88; N, 15.83. $C_{15}H_{12}BN_3O$ calcd.: C, 69.00; H, 4.63; N, 16.10%.)

3-p-Tolyl-5-isoxazoleboronic acid (Ib)

This was similarly obtained in 60% yield from *p*-tolunitrile oxide (m.p.⁸ 55–56°) (ethereal solution prepared from 7.0 g of *p*-tolylhydroxamyl chloride) and dibutyl ethynylboronate (6.0 g). Colourless needles (from 50% aq. methanol or chloroform), m.p. 121° dec. (Found: C, 59.06; H, 5.17; N, 7.00. $C_{10}H_{10}BNO_3$ calcd.: C, 59.16; H, 4.96; N, 6.90%.) UV spectrum: $\lambda_{max} = 248 \text{ m}\mu$; $\log \epsilon = 4.16$.

3-(p-Bromophenyl)isoxazole-5-boronic acid (Ic)

This was similarly obtained from *p*-bromobenzonitrile oxide⁹ (3.1 g) and dibutyl ethynylboronate (2.8 g) in ether. Some 3,4-bis(*p*-bromophenyl)furoxan, m.p. 162–164° (1.5 g), and impure product, m.p. 130–132° (1.7 g) were isolated. Recrystallization of the latter from methanol gave colourless needles, m.p. 147–148° dec. (Found: Br, 29.54; N, 5.14. C₉H₇BBrNO₃ calcd.: Br, 29.82; N, 5.22 %.) UV spectrum: $\lambda_{max} = 251 \text{ m}\mu$; $\log \epsilon = 4.30$.

Alkaline deboronation

3-Phenyl-5-isoxazoleboronic acid (750 mg) was boiled for 5–7 min with 30 ml of 14% aqueous NaOH, to give an oil, which was steam-distilled. Extraction of the distillate with ether, drying of the organic layer and removal of the solvent yielded 500 mg of 3-phenylisoxazole (IIa), identical with an authentic sample^{10,11}.

3-*p*-Tolyl-5-isoxazoleboronic acid, analogously treated for 15 minutes with 10% NaOH, yielded a liquid, b.p. 86°/0.2 mm, which solidified to give white crystals, m.p. 37°. (Found: C, 75.58; H, 5.88; N, 8.86. C₁₀H₉NO calcd.: C, 75.45; H, 5.70; N, 8.80 %.) These were identified as 3-*p*-tolylisoxazole (IIb) by comparison with an authentic sample prepared by the following route: (i) 3-*p*-tolyl-5-acetoxy-2-isoxazoline was isolated in 38% yield from the cycloaddition of *p*-tolunitrile oxide to vinyl acetate in ether. Colourless plates, m.p. 88–89° (from hexane). (Found: C, 65.97; H, 6.14; N, 6.54. C₁₂H₁₃NO₃ calcd.: C, 65.74; H, 5.98; N, 6.39 %.) (ii) Boiling of the above 2-isoxazoline with conc. HCl led to an oil which was distilled at 107–110°/3 mm. A 52% yield of a colourless liquid was obtained, which on cooling slowly gave crystals, m.p. 37° after sublimation. UV spectrum: $\lambda_{max} = 246 \text{ m}\mu$; $\log \epsilon = 4.19$.

3-(*p*-Bromophenyl)-5-isoxazoleboronic acid, boiled with 10% NaOH for 3–5 minutes, gave a 83% yield of 3-(*p*-bromophenyl)isoxazole (IIc), m.p. 101°, identical with a sample prepared by the following route: (i) condensation of *p*-bromobenzonitrile oxide with an excess of vinyl acetate in ether led to a 97% yield of 3-*p*-bromophenyl-5-acetoxy-2-isoxazoline, m.p. 101°. (Found: C, 46.76; H, 3.37; Br, 28.78; N, 5.02 %. C₁₁H₁₀BrNO₃ calcd.: C, 46.45; H, 3.55; Br, 28.13; N, 4.93 %.) (ii) Acid hydrolysis and dehydration of this product afforded 3-*p*-bromophenylisoxazole, m.p. 101° (from methanol), in 78% yield. (Found: C, 48.82; H, 2.68; Br, 35.17; N, 6.15. C₉H₆BrNO calcd.: C, 48.24; H, 2.69; Br, 35.67; N, 6.25 %.) The UV spectrum ($\lambda_{max} = 251 \text{ m}\mu$; $\log \epsilon = 4.32$) has been already reported¹².

Oxidative deboronation

Heating (Ia) (48 mg) in ethanol (1 ml) with 30% hydrogen peroxide (0.1 ml) for 5 min followed by dilution with water yielded 3-phenyl-5-isoxazolone (IIIa) (18 mg, 44%), m.p. 151–152° dec., identical with an authentic sample¹³.

Analogous treatment of (Ib) with 30% hydrogen peroxide gave 3-*p*-tolyl-5-isoxazolone (IIIb), m.p. 132° (from dil. MeOH) in 85% yield (lit.¹⁴: m.p. 131–133°).

Analogously from (Ic) and 30% H₂O₂ 3-(*p*-bromophenyl)-5-isoxazolone (IIIc), m.p. 164–165° (from ethanol), was obtained in 81% yield. The product was identical with an authentic sample prepared by a different route¹⁵.

Bromination

A solution of *N*-bromosuccinimide (467 mg) in *N,N*-dimethylformamide was

added dropwise to a stirred solution of (Ia) (495 mg) in the same solvent (1 ml). The reaction mixture was left at room temperature for 24 h, then diluted with cold water. The precipitate (567 mg, 81%) was filtered and dried: colourless crystals, m.p. 116° dec. (after washing with ether/n-pentane). The product could not be crystallized because of its instability to heat (Found: C, 40.27; H, 2.82; Br, 29.87; N, 5.29. $C_9H_7BBrNO_3$ calcd.: C, 40.34; H, 2.64; Br, 29.83; N, 5.23%.) UV spectrum: $\lambda_{max} = 239 m\mu$; $\log \epsilon = 3.90$. It was shown to be 3-phenyl-4-bromo-5-isoxazoleboronic acid (IVa) by alkaline deboronation with 5% aq. NaOH to 3-phenyl-4-bromoisoxazole (Va), m.p. 60–60.5° (lit.¹⁶: m.p. 50–51°), identical with an authentic sample prepared by bromination of 3-phenylisoxazole¹⁶. The 4-position of the bromine atom was demonstrated by permanganate oxidation, which gave benzoic acid.

A solution of (Ib) (613 mg) in N,N-dimethylformamide was treated as above with N-bromosuccinimide (537 mg), to give 3-*p*-tolyl-4-bromo-5-isoxazoleboronic acid (IVb) (590 mg; 70%), m.p. 116° dec. (Found: Br, 28.39; N, 5.01. $C_{10}H_9BBrNO_3$ calcd.: Br, 28.35; N, 4.96%.) Alkaline deboronation with cold dilute NaOH gave an oil, b.p. 119°/0.3 mm. The product was identical with a sample of 3-*p*-tolyl-4-bromoisoxazole (Vb), obtained by direct bromination of 3-*p*-tolylisoxazole with Br_2 in HNO_3 (d 1.52). (Found: C, 49.95; H, 3.43; Br, 33.17; N, 5.64. $C_{10}H_9BrNO$ calcd.: C, 50.44; H, 3.38; Br, 33.58; N, 5.88%.)

A solution of (Ic) (400 mg) in dimethylformamide, treated likewise with N-bromosuccinimide (266 mg), gave 3-(*p*-bromophenyl)-4-bromo-5-isoxazoleboronic acid (IVc) (470 mg; 90%), m.p. 136° dec. (Found: Br, 46.00; N, 3.80. $C_9H_6BBrNO_3$ calcd.: Br, 46.09; N, 4.04%.) Alkaline deboronation with cold dil. NaOH yielded 3-(*p*-bromophenyl)-4-bromoisoxazole (Vc), needles, m.p. 84° (from n-pentane), identical with a sample prepared by direct bromination of 3-(*p*-bromophenyl)isoxazole with Br_2/HNO_3 . (Found: C, 35.90; H, 1.78; Br, 53.66; N, 4.60. $C_9H_5Br_2NO$ calcd.: C, 35.68; H, 1.66; Br, 52.76; N, 4.62%.) The oxidation of (Vc) with $KMnO_4$ on steam bath gave *p*-bromobenzoic acid with 43% yield.

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SUMMARY

3-Aryl-5-isoxazoleboronic acids have been prepared by cycloaddition of aryl-nitrile oxides to dibutyl ethynylboronate. Some of their chemical properties and reactions leading to known isoxazole derivatives, are described.

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