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SYNTHESIS OF 4-ISOXAZOLEBORONIC ACIDS: A NEW ROUTE TO 4-ISOXAZOLONES*

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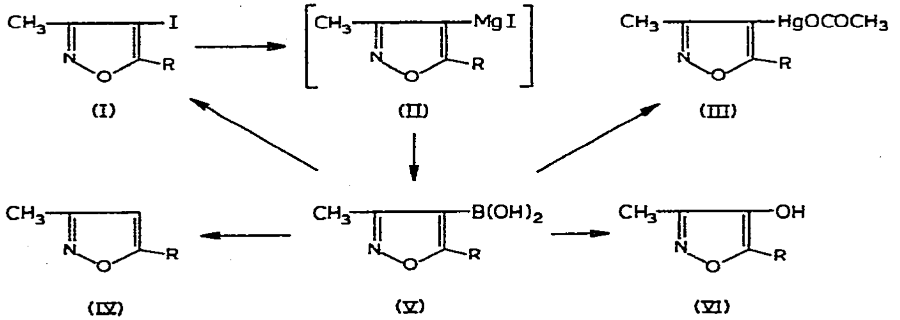
Pursuing our studies on isoxazoleboronic acids[1], we report here the synthesis of the hitherto unknown 4-isoxazoleboronic acids. Whereas 3- and 5-isoxazolylmagnesium halides have not been prepared up to now, some 4-isoxazolylmagnesium iodides have been successfully used to synthesize 4-isoxazole carbinols and acids[2-4].

Treatment of 3,5-dimethyl-4-isoxazolylmagnesium iodide (IIa) with trimethyl borate gave 3,5-isoxazole-4-boronic acid (Va) in fair yield. The structure was proved by the following reactions: (*a*) Treatment with diethanolamine gave the expected cyclic ester. (*b*) Alkaline hydrolysis led to 3,5-dimethylisoxazole (IVa), isolated through its cadmium chloride salt. (*c*) Sodium hypoiodide transformed the acid in 3,5-dimethyl-4-iodoisoxazole (Ia). (*d*) Oxidation with hydrogen peroxide led to the already known 3,5-dimethyl-4-isoxazolone, which is present in the OH form (VIa)[5]. (*e*) Treatment with mercuric acetate gave immediate separation of 3,5-dimethyl-4-isoxazolylmercuric acetate (IIIa).

No attempt was made to isolate the intermediate dimethyl boronate.



a : R = CH_3 ; b : R = C_6H_5

The synthesis was extended to 3-methyl-5-phenyl-4-isoxazolylmagnesium iodide (IIb), equally prepared by entrainment reaction of 3-methyl-5-phenyl-4-iodoisoxazole (Ib) with magnesium in the presence of ethyl bromide. Treatment of the Grignard reagent with tributyl borate gave 3-methyl-5-phenyl-4-isoxazoleboronic acid (Vb), whose structure was assured by an analogous set of reactions as above.

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In this case yields were lower than in the former one; the Grignard reagent from 3,5-diphenyl-4-iodoisoxazole gave still lower, almost insignificant, yields of boronic acid.

The 4-isoxazolones hitherto known have been prepared by two different, rather long and tedious, methods, either from 2-acetoxy-1,3-diketones and hydroxylamine[5,6] or from 4-isoxazolediazonium salts[7]; the present synthesis through the isoxazoleboronic acids represents an alternative route to this interesting, still little studied, class of compounds.

EXPERIMENTAL

All m.p.'s are uncorrected. Microanalyses were performed by Dr. LUCIA MAGGI DACREMA.

3,5-*Dimethyl-4-isoxazoleboronic acid* (*Va*)

To a stirred suspension of magnesium turnings (9.75 g) in a mixture (150 ml) of anhydrous diethyl ether and tetrahydrofuran, containing some ethyl bromide (3.74 ml), a solution of 3,5-dimethyl-4-iodoisoxazole (30.0 g)[8] and ethyl bromide (17.4 ml in tetrahydrofuran) was added dropwise under nitrogen. After maintaining the mixture at 40° until total disappearance of magnesium, the emulsion was transferred under nitrogen to a separatory funnel and dropped on a stirred solution, precooled at −15°, of trimethyl borate (53 ml) in anhydrous ether (150 ml). Always maintaining the temperature at −15°, stirring was continued for further 4 h. After decomposing with 10% aq. hydrochloric acid (150 ml) and saturated sodium chloride solution (80 ml), the organic layer was separated and the aqueous layer extracted several times with ether. The united extracts were evaporated and the residue was crystallized from aqueous methanol, yielding colourless prisms (8.5 g), m.p. 122°. (Found: C, 42.47; H, 5.61; N, 10.15. $C_5H_8BNO_3$ calcd.: C, 42.61; H, 5.72; N, 9.93%.)

Use of lower temperature (−70°) or of ethylene bromide instead of ethyl bromide did not improve the yield.

Esterification of (Va) with diethanolamine in ether led quantitatively to the cyclic ester, white crystals, m.p. 240°. (Found: C, 51.72; H, 7.18; N, 13.14. $C_9H_{15}BN_2O_3$ calcd.: C, 51.46; H, 7.19; N, 13.34%.)

3-*Methyl-5-phenyl-4-isoxazoleboronic acid* (*Vb*)

The Grignard reagent was prepared as above from magnesium (8.1 g), ethyl bromide (16.4 ml) and 3-methyl-5-phenyl-4-iodoisoxazole (30.0 g)[8], using tetrahydrofuran as solvent. After addition to trimethyl borate (45 ml) at −15°, the ethereal extracts were treated with a slight excess of 7.5% aq. sodium hydroxide. From the organic layer 3-methyl-5-phenylisoxazole (11.8 g) was isolated, whereas acidification of the alkaline solution yielded the boronic acid (5.0 g), m.p. 118°. After recrystallisation from aq. methanol colourless plates, m.p. 124–125°. (Found: C, 59.33; H, 5.42; N, 6.89. $C_{10}H_{10}BNO_3$ calcd.: C, 59.16; H, 4.96; N, 6.90%.)

Esterification of the above product with diethanolamine yielded the cyclic ester, m.p. 198–200°. (Found C, 61.50; H, 6.01; N, 10.50. $C_{14}H_{17}BN_2O_3$ calcd.: C, 61.69; H, 6.32; N, 10.30%.)

Alkaline deboronation

After treatment of (Va) (1.0 g) with 10% aq. sodium hydroxide (20 ml), the reaction mixture was steam-distilled. The first fraction (40 ml) of distillate was treated with a saturated solution of cadmium chloride. The precipitated solid (0.26 g) was filtered and decomposed upon heating, yielding 3,5-dimethylisoxazole (IVa) (70 mg), identical with an authentic sample.

Brief boiling of (Vb) with aq. sodium hydroxide gave 3-methyl-5-phenylisoxazole, m.p. 64–65°, in 76% yield. The product is identical in every respect with an authentic sample.

3,5-*Dimethyl-4-iodoisoxazole* (*Ia*)

To a stirred suspension of (Va) (500 mg) in 14% aq. sodium hydroxide (14 ml) iodine (1.8 g) was added in small portions. After stirring for further 2 h, the precipitated (Ia) was filtered (208 mg) and crystallized from methanol, m.p. and mixed m.p. 51.5–53°.

3-*Methyl-5-phenyl-4-iodoisoxazole* (*Ib*)

Analogous treatment of (Vb) with sodium hydroxide and iodine afforded (Ib), m.p. and mixed m.p. 65–66°, in 71% yield.

3,5-*Dimethyl-4-isoxazolylmercuric acetate* (*IIIa*)

Adding a cold solution of mercuric acetate (0.25 g) to a solution of (Va) (0.1 g) in aq. ethanol caused immediate separation of colourless needles (0.22 g), m.p. 179–180°. (Found: C, 23.80; H, 2.72; Hg, 56.31; N, 3.96. $C_7H_9HgNO_3$ calcd.: C, 23.63; H, 2.54; Hg, 56.39; N, 3.93%.) The product is identical in every respect to 3,5-dimethyl-4-isoxazolylmercuric acetate, m.p. 179–180°, prepared according to the literature[9]. However the m.p. given in lit. is 104–105°.

3-*Methyl-5-phenyl-4-isoxazolylmercuric acetate* (*IIIb*)

(*a*) Analogous treatment of the boronic acid (Vb) with mercuric acetate gave a 82% yield of colourless crystals, m.p. 167–168°. (Found: C, 34.69; H, 2.83; Hg, 47.22; N, 3.47. $C_{12}H_{11}HgNO_3$ calcd.: C, 34.57; H, 2.65; Hg, 48.01; N, 3.35%.)

(*b*) Heating for 1 h on steam bath an equimolecular mixture of 3-methyl-5-phenylisoxazole and mercuric acetate gave an almost quantitative yield of crystals, m.p. 167–168°, identical with the product prepared by method (*a*).

3,5-*Dimethyl-4-isoxazolone* (*VIa*)

To a stirred solution of 3,5-dimethyl-4-isoxazoleboronic acid (1.0 g) in little anhydrous ethanol 30% hydrogen peroxide (0.7 ml) was cautiously added, maintaining the temperature of the reaction mixture below 40°. After diluting with water, ether extraction, drying and solvent evaporation, the residue (0.37 g), m.p. 76–78°, was recrystallised from water to give white needles, m.p. 79°, identical with an authentic sample of 3,5-dimethyl-4-isoxazolone[5].

3-*Methyl-5-phenyl-4-isoxazolone* (*VIb*)

Analogous treatment of (Vb) with 30% hydrogen peroxide afforded a 46% yield of white crystals, m.p. 96° (from aq. methanol), having acidic properties. (Found:

C, 68.59; H, 5.36; N, 8.20. $C_{10}H_9NO_2$ calcd.: C, 68.56; H, 5.18; N, 8.00%.) The product gives an emerald-green ferric chloride colouration.

SUMMARY

4-Isoxazoleboronic acids have been prepared by interaction of 4-isoxazolylmagnesium iodides with trimethyl borate. Some of their reactions are described; in particular oxidative deboronation represents a new useful route to 4-isoxazolones.

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