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N-SUBSTITUTED-2-CARBOXAMIDOPHENYLBORONIC ACID ANHYDRIDES

JANINA ALTMAN *, HELMUT BÖHNKE, ALOIS STEIGEL and GÜNTER WULFF*

Institute of Organic Chemistry II of the University of Düsseldorf, Universitätsstr. 1, D-4000 Düsseldorf (F.R.G.)

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Summary

N-Substituted-2-carboxamidophenylboronic acid anhydrides were prepared by lithiation of 2-phenyl-2-oxazolines and subsequent reaction with trimethyl borate or borane, followed by hydrolysis. The hydrolysis is very rapid owing to a strong neighbouring group effect.

Introduction

Growing interest in arylboronic acids arising from their use in elaborating polymers with chiral cavities and in affinity chromatography [1] prompted us to synthesize *ortho*-carboxyphenylboronic acid derivatives. The *meta* and *para* isomers had been prepared previously by permanganate oxidation of the corresponding toluenes [2], but the more interesting *ortho* isomer was still unknown. *ortho*-Tolueneboronic acid has been shown by others [3] to yield only benzoic acid upon oxidation.

Results and discussion

Our approach was based on the ability of the 2-phenyl-2-oxazoline system to serve as a masking group for the carboxylic function and on its ability to undergo metallation in the *ortho* position with subsequent reaction with electrophiles [4]. In our case the boronic acid function was introduced by use of $B(OMe)_3$ or BH_3 as the electrophile.

The fast metallation of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (**1a**) via lithium halogen exchange at −75°C [5] or a direct lithiation of 2-(4-chlorophenyl)-4,4-dimethyl-2-oxazoline (**1b**) at −15°C [6] led to yellow-brownish complex **2** which was quenched with an excess of trimethyl borate or borane. The resulting intermediate 2-oxazolinylphenylboronic acid dimethyl ester (**3**) was detected in NMR and in the mass spectrum of the product mixture prior to hydrolysis.

* On leave from the Department of Biophysics, The Weizmann Institute of Science, Rehovot (Israel).

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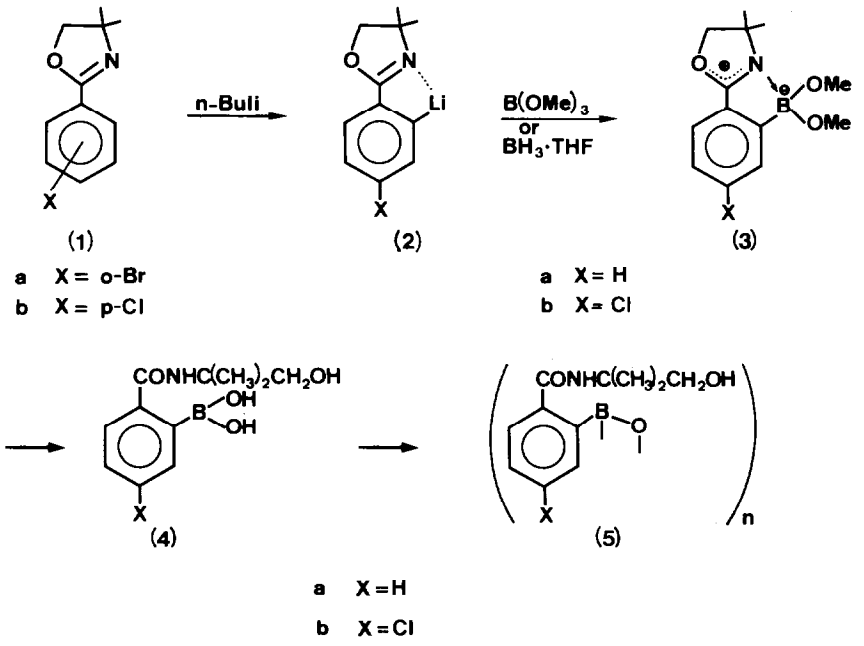
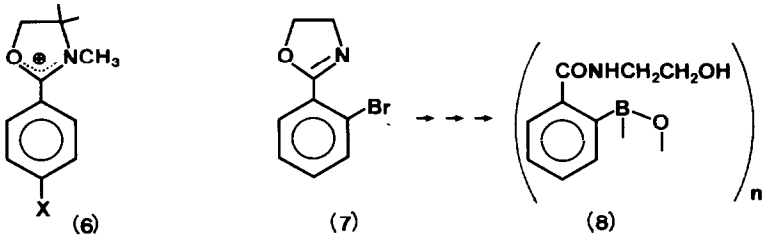


SCHEME 1

In the ^{1}H NMR spectrum the signal of CH_2O protons of **3a** (4.17 ppm) is shifted downfield compared with that of the parent oxazoline **1a** (4.08 ppm). A strong downfield shift of CH_2O protons of nearly 1 ppm unit is observed when oxazolin **1b** is transformed to methyl oxazolinium iodide **6**. In the ^{13}C NMR spectrum the CH_2O carbon signal of **3a** appears between those of the parent oxazoline **1a** and the oxazolinium salt **6** (see Table 1). These data point to the presence of a partial positive charge on the oxazoline ring in **3a** arising from the B–N interaction.

It was found that **3** is very sensitive to nucleophilic ring opening. Thus upon addition of water at room temperature an extremely rapid ring opening to give an carboxamido group occurs. In this respect **3** is even more reactive than oxazolinium salt **6a** which was prepared for its ease of hydrolysis and which is reported to undergo ring opening during 1–2 h at 70–90°C [7]. Therefore the zwitterionic



SCHEME 2

nature of **3** cannot be the only reason for this extreme reactivity but some additional effect of the neighbouring boron must be assumed.

After neutralization with solid NH_4Cl, hydrolysis with cold water and extraction with ethyl acetate the spontaneously formed anhydride **5a**, repectively, **5b** precipitated upon standing in 70–80% yield. The absence of a strong B–OH absorption in 3250–3400 cm^{-1} region [8] of air-dried samples of **5a** and **5b** supports the assumption of their anhydride nature. In the case of **5b**, the free hydroxyl group, was acetylated with acetic anhydride in pyridine to yield the monoacetate.

1,3-Bis-(4,4-dimethyl-2-oxazolinyl)benzene was found to undergo lithiation in the *ortho* positions of both oxazoline rings, as revealed by quenching with D_2O or CH_3I [9], but the lithium derivative failed to react with $B(OMe)_3$ or BH_3. This again shows that reactions at the boron atom are very sensitive to steric requirements.

A similar reaction sequence starting from **7** gave **8** in 23% yield. In contrast to **5a** and **5b**, **8** is soluble in water and in hydroxylic solvents, and so better NMR spectra could be obtained. In CD_3OD **8** must be present as the dimethyl ester, but this should not affect structural assignments. The protons of the oxazoline ring in **7** exhibit in the ^1H NMR spectrum (CD_3OD) a complex AA'BB' pattern in 4.7–3.8 ppm region, and in the boronated open-chain product **8** this is, as expected, reduced to two partially overlapping triplets between 3.92–3.62 ppm. The ^{11}B NMR spectrum shows a single peak at 26.6 ppm, characteristic of an uncoordinated boronic acid function.

In the case of **5a** and **5b**, ^{13}C NMR appeared to be a better tool for detection of the open-chain structure than ^1H NMR, although owing to low solubility the spectra are not of a very good quality. The signal for the C=O carbon is shifted by 10 ppm downfield from that of cyclic C=N (see Table 1). Furthermore there is an

TABLE 1

^{13}C NMR DATA FOR *N*-SUBSTITUTED-2-CARBOXAMIDOPHENYLBORONIC ACID ANHYDRIDES AND SOME RELATED COMPOUNDS

Compound	*C*=O or *C*=N	CH_2O	*C*N	CCH_3
1a	161.30	79.13	67.90	28.15
1b	160.86	79.07	67.59	28.31
1c	161.73	78.91	67.41	28.34
3a	164.28	81.00	66.44	28.03
5a [a]	172.01	68.79	56.14	24.05
5b [a]	170.52	68.62	56.31	23.98
6	169.92	81.71	68.93	24.61
$CONHC(CH_3)_2CH_2OH$ | C_6H_5	168.80	70.24	55.88	24.00
$CONHC(CH_3)_2CH_2OH$ | C_6H_4Cl	167.19	70.13	56.06	24.04
7	163.30	67.43	55.24	
8 [b]	173.96	60.78	45.20	
$CH_3CONHCH_2CH_2OH$ [c]		60.3	42.0	

[a] In pyridine-d_5. Owing to the low concentrations in pyridine the recorded spectra may be those of the acids. [b] In CD_3OD. Under these conditions **8** will be mainly present as its dimethyl ester. All others in $CDCl_3$. [c] Sadtler Standard Carbon-13-NMR-Catalogue.

upfield shift of 11 ppm for both the quarternary carbon and the CH_2O carbon. In ^1H NMR spectra of the boronated compounds **5a** and **5b** as well as **8** exhibit a characteristic downfield shift from 7.3–7.8 to 8.1–8.2 ppm for the aromatic proton *ortho* to the boronic acid function.

The very low solubilities in organic solvents prevented molecular weight determination, and so distinction between dimeric or trimeric anhydride was not possible [10]. In the mass spectra (electron impact) **5a** has a peak at *m/e* 201 (10.9%), **5b** one at 235 (9.6%) and **8** one at 173, corresponding to a monomeric $M - 18$ ion fragment. After prolonged exposure small peaks of dimeric anhydride appear at *m/e* 402 and 470 ($2M - 36$) (0.52%) respectively, and very weak ions from the trimeric anhydrides ($3M - 54$) were also observed. Other mass spectroscopic techniques which normally produce less fragmentation, such as chemical ionisation (i-butane), field desorption, and fast-atom bombardment (Xe), gave similar results. The results did not permit distinction between the dimeric or trimeric anhydride structure (see also ref. [10]).

The boronic acid function in *ortho* carboxamido derivatives appears to be more sensitive to deboronation than that in the *ortho*-alkylamino substituted compounds [11]. Deboronation was detected upon heating with hydroxylic solvents under standard conditions for esterification.

In summary, 2-carboxamidophenylboronic acid derivatives can now be made by introduction of the boronic acid function into simple 2-phenyl-2-oxazoline systems. More elaborate chiral oxazolines may give optically active derivatives.

Experimental

Melting points were determined on a Büchi 510 melting-point apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1420 spectrophotometer. ^1H NMR spectra were recorded on a Bruker WP-80 spectrometer and ^{13}C NMR spectra on a Varian XL 100 instrument. All reactions were performed under dry N_2.

2-N(1,1-Dimethyl-2-hydroxyethyl)carboxamidophenylboronic acid anhydride (5a)

A solution of 2(2-bromophenyl)-4,4-dimethyl-2-oxazoline (**1a**) (prepared by the thionylchloride method [12]) (1.27 g, 5 mmol) in dry ether (15 ml) was cooled to −78°C and n-butyllithium 1.6 *M* in hexane (3.5 ml, 5.5 mmol) was slowly added. The mixture, containing the yellow lithiated complex **2a**, was stirred for 30 min, then siphoned into a flask containing trimethyl borate (2.08 g, 20 mmol) in ether (10 ml) precooled to −78°C. After 5 min the yellow colour disappeared and the mixture was stirred in an ice bath for 15 min, then NH_4Cl (1 g) was added, followed by cold water (25 ml) and ethyl acetate (50 ml). The mixture was stirred for 10 min then the organic layer was separated, washed twice with cold water (10 ml), and set aside overnight at room temperature. The boronic acid **4a** which had formed was spontaneously converted into the spairingly soluble anhydride **5a**, which separated as an amorphous solid, m.p. 214°C, (740 mg, 70%); IR (KBr) cm^{-1}: 1635, 1605, 1540, 1360; ^1H NMR (pyr-d_6): 8.17 (d br, 2H, ArH), 7.81 (d, *J* 7 Hz, 1H, ArH), 7.37 (q, *J* 7 and 2 Hz, 1 H, ArH), 4.05 (s, 2H, CH_2), 1.65 (s, 6H, CH_3), Anal. Found: C, 60.59; H, 6.78; N, 6.07. $C_{11}H_{14}BNO_3$ calcd.: C, 60.31; H, 6.44; N, 6.39%).

5a was also obtained in 70–80% yield when a precooled 1 *M* solution of borane in THF (6 ml) was used instead of $B(OCH_3)_3$, with work up as before.

For spectroscopic characterisation of **3a**, **1a** (2.54 g, 10 mmol) was lithiated as above using 9 mmol of BuLi. After quenching with $B(OMe)_3$ (5.5 g, 53 mmol), the ether and the excess of $B(OMe)_3$ were distilled off under reduced pressure at −10°C. The residue was extracted with methylene chloride, and the extract was concentrated at −10°C to yield 2-(4,4-*dimethyl*-2-*oxazolinyl*)*phenylboronic acid dimethyl ester* (*3a*) together with the unchanged bromide, in the approximate ratio 3/2 as estimated by ^1H NMR; traces of debrominated 2-phenyl-4,4-dimethyl-2-oxazoline (**1c**, X = H) were also detected, probably formed from **2a** by proton abstraction. ^1H NMR ($CDCl_3$) of **3a**: 8.05–7.90 (m, 1H, ArH, *ortho* to B), 7.7–7.2 (m, 3H, ArH), 4.17 (s, 2H, CH_2O), 3.46 (s, 3H, OCH_3), 1.40 (s, 3H, CH_3). MS: *m/e* 246.

2-N(1,1-Dimethyl-2-hydroxyethyl)carboxamido-5-chlorophenylboronic acid anhydride (5b)

By the procedure described for reaction of **1a**, 2-(4-chlorophenyl)-4,4-dimethyl-2-oxazoline (**1b**) (prepared by the thionyl chloride method [12], b.p. 98°C/20 mmHg, m.p. 35–37°C, Lit. [13]: b.p. 70°C/0.4 mmHg, m.p. 24°C) (5.25 g, 25 mmol) was converted into the anhydride **5b** (5.22 g, 82%), m.p. 228°C, IR (KBr) cm^{-1}: 1635, 1602, 1540, 1360. ^1H NMR (pyr-d_5): 8.4 (br. s, 1H, NH), 8.10 (d, *J* 2 Hz, 1H, ArH *ortho* to B), 7.88 (d, *J* 8 Hz, 1H, ArH), 7.35 (q, *J* 8 and 2 Hz, 1H, ArH), 4.08 (s, 2H, CH_2O), 1.65 (s, 6H, CH_3). Anal. Found: C, 52.05; H, 5.32; N, 5.39. $C_{11}H_{13}BClNO_3$ calcd.: C, 52.12; H, 5.12; N, 5.52%. MS (electron impact) *m/e*: 235 (*M* − 18, 9.66%); 220 (*M* − 33, 100%). Upon prolonged exposure *m/e* 440 and 470 (2*M* − 36, 0.5%) as well as traces of 705 were also detected.

Compound **5b** (127 mg, 0.5 mmol) was acetylated by stirring overnight a suspension in dry pyridine (5 ml) containing acetic anhydride (204 mg, 2 mmol). A homogeneous solution was obtained, and from this pyridine was distilled off at room temperature, then ethyl acetate (10 ml) was added and the solution was centrifuged to remove some insoluble solid (23 mg), washed 3 times with water (5 ml), concentrated, then dried under high vacuum. The oily residue solidified upon standing. IR (KBr) cm^{-1}: 1735 ($OCOCH_3$), 1625 (CONH). ^1H NMR ($CDCl_3$): 7.88 (d, *J* 2 Hz, 1H, ArH), 7.50 (d, *J* 8 Hz, 1H, ArH), 7.28 (*J* 8 and 2 Hz, 1H, ArH), 6.70 (br, s, 1H, NH), 4.25 (s, 2H, CH_2OCO), 2.00 (s, 3H, CH_3), 1.40 (s, 6H, CH_3).

2-(4-Chlorophenyl)3,4,4-trimethyl-2-oxazoliniumiodide (6b)

To a solution of **1b** (1.04 g, 5 mmol) in nitromethane (7 ml) was added CH_3I (1.06 g, 7.5 mmol). The mixture was kept in a bath at 80°C for 4 h, then cooled, and dry ether (40 ml) was added. The product **6b** which separated was recrystallized from methanol/ethyl acetate (835 mg) m.p. 178–180°C. ^1H NMR ($CDCl_3$): 8.20 and 7.65 (A_2B_2, *J* 8 Hz, 4H, ArH), 5.10 (s, 2H, CH_2O), 3.62 (s, 3H, CH_3N), 1.82 (s, 6H, CH_3). Anal. Found: C, 40.88; H, 4.15; N, 3.96. $C_{12}H_{15}ClINO$ calcd.: C, 40.99; H, 4.30; N, 3.98%).

2-(2-Bromophenyl)-2-oxazoline (7)

2-Bromobenzoyl chloride (22 g, 0.1 mol) in dichloromethane (50 ml) was slowly added to an ice-cooled solution of ethanolamine (6.1 g, 0.1 mol) and triethylamine (10.1 g/0.1 mol) in dichloro methane (50 ml) and the mixture was stirred for 3 h at

room temperature. The solvent was evaporated off and the crude amino alcohol was extracted with ethyl acetate (150 ml). The extract was filtered to remove $Et_3N \cdot HCl$ then concentrated, and the solid was redissolved in dichloromethane (100 ml). The solution was cooled in an ice-salt bath and $SOCl_2$ (42 g, 0.3 mol) was slowly added. The mixture was left overnight at 0°C, then dry ether (500 ml) was added to precipitate crude oxazoline hydrochloride (11 g). The salt was dissolved in cold water and the solution brought to pH 11 with 3*N* NaOH. Product **7** was extracted with CH_2Cl_2, and the extract was dried, and evaporated and the residue distilled, b.p. 79°C/0.2 mmHg (7.5 g, 38%), IR ($CHCl_3$) cm^{-1}: 1655. ^1H NMR (CD_3OD). 7.82–7.32 (m, 4H, ArH), 4.70–4.40 (m, 2H, CH_2O), 4.20–3.82 (m, 2H, CH_2N). Anal. Found: C, 47.90; H, 3.68; N, 6.14. C_9H_8BrNO calcd.: C, 47.81; H, 3.56; N, 6.19%.

*2-N(2-Hydroxyethyl)carboxamidophenylboronic acid anhydride (**8**)*

Compound **8** was prepared similarly starting from **7** (1.13 g, 5 mmol), 1.55 *M* BuLi in hexane (3.6 ml, 5.5 mmol) and trimethyl borate (3 ml). Compound **8** precipitated out from the concentrated ethyl acetate solution, m.p. 235–240°C (220 mg, 23%). IR (KBr) cm^{-1}: 1640. ^1H NMR (CD_3OD): 8.20 (d, *J* 8 Hz, 1H, ArH), 7.38–7.75 (m, 3H, ArH), 3.92–3.62 (m, 4H, OCH_2CH_2N). Anal. Found: C, 56.54; H, 5.38; N, 7.02. $C_9H_{10}BNO_3$ calcd.: C. 56.59; H, 5.29; N, 7.33%.

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