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REACTIONS OF BOROXAZOLIDONES WITH AROMATIC ALDEHYDES

AN EASY ROUTE TO DERIVATIVES OF ISOQUINOLINE AND ISO-INDOLINONE

G. H. L. NEFKENS and B. ZWANENBURG*
Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

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Abstract—Boroxazolidones **1** derived from glycine and phenylalanine react with aromatic aldehydes to form the corresponding imines. The product **3** from **1a** with *o*-carboxybenzaldehyde is converted into 4-hydroxyisoquinoline-3-carboxylic acid **6** by dimethyl sulfate, followed by t-BuOK, and aqueous acid.

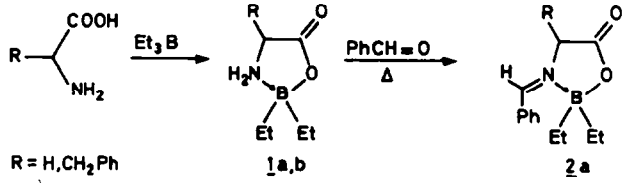
With *o*-phthalaldehyde and **1a,b** the isoindolinones **11a,b** are obtained. These reactions proceed via carboxylic acids **9**. Compound **9a** was also prepared from **3** by catalytic hydrogenation. Salicylaldehyde and **1a** gave polymeric material, but the preformed Schiff's base **13** can be transformed into the *p*-nitrobenzyl ester **15** by treatment successively with dicyclohexylamine, triethylborane and *p*-nitrobenzyl bromide.

A variety of boroxazolidones[1] can readily be prepared by the reaction of α-aminoacids with trialkylboranes[2,6,7] (cf. Scheme 1). These boron compounds of the type **1** show a strong intramolecular coordination between boron and the amino group. In a previous paper[7] we have described the use of these heterocycles for the simultaneous protection of the α-amino and the carboxyl function in α-amino acids. This paper deals with the question whether the strongly coordinated nitrogen atom in the boroxazolidones still has nucleophilic properties. In this context we investigated the reaction of some boroxazolidones with aromatic aldehydes in order to find out if the formation of Schiff's bases can be accomplished.

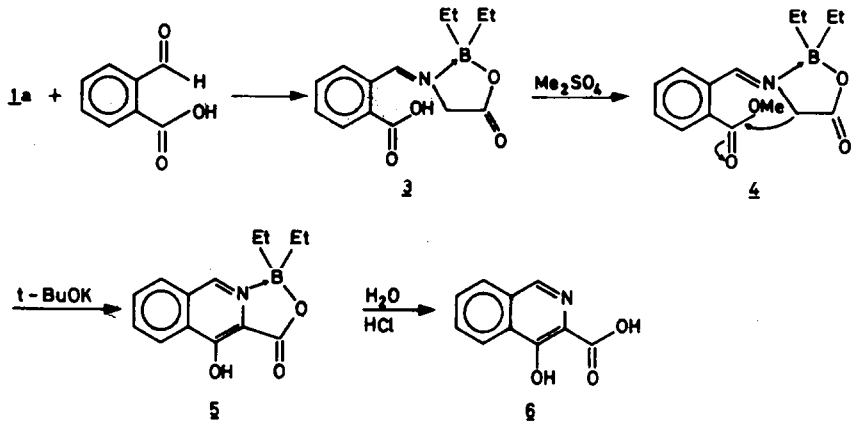
Heating of boroxazolidone **1a** (prepared from glycine and triethylborane) with benzaldehyde in benzene and with azeotropic removal of water produced the imine **2a** in 60% yield (Scheme 1). This result shows that in spite of the strong intramolecular coordination the amino function in **1** still can react as a nucleophile with a carbonyl group.

Three *ortho*-substituted benzaldehydes were selected for this study with the expectation that the substituents might interact with the boroxazolidone ring. With *o*-carboxybenzaldehyde and **1a** a smooth reaction took place, giving product **3** in good yield (Scheme 2). This Schiff's base could easily be converted into the methyl ester **4** (Me_2SO_4). Treatment of **3** with *p*-nitrophenol and dicyclohexylcarbodiimide gave the corresponding *p*-nitrophenyl ester. By treatment of ester **4** with potassium t-butoxide an intramolecular condensation took place producing the boron complex **5** of an isoquinoline derivative. Deboration was readily accomplished (H^+/H_2O or 8-hydroxyquinoline) to give the isoquinoline **6** (Scheme 2). Compound **6** had earlier been prepared by Kim and Mamaev[8] in moderate yield starting from ethyl *o*-chloromethylbenzoate and ethyl *N*-tosylglycinate.

By reaction of boroxazolidones **1a,b** with *o*-phthalaldehyde at reflux temperature the products **11a,b** were obtained. Compound **11a** (not optically active) has previously been prepared by a Clemmensen reduction of ethyl phthalimidoacetate.[9] The formation of compounds **11** from **1** can be rationalized as outlined in Scheme 3. The initially formed Schiff's base **7** adds water (produced during the imine formation) at the aldehyde function to give **8**. Then an intramolecular Cannizzaro-type reaction leads to the carboxyl acid **9** which undergoes ring-closure to the amide boron complex **10**. This boroxazolidone, formally derived from an *N*-acyl amino acid, readily deborates[10] under the conditions of the reaction to give isoindolinone **11**. The unexpected hydride transfer during the conversion of **8** into **9** is somewhat similar to the hydride shift suggested by Yamamota *et al.*[11] for their synthesis of isoindolinones from phthalaldehyde and isocyanates. Support for the sequence shown in Scheme 3 is provided by the independent synthesis of **11a** from carboxylic acid **3**



Scheme 1.



Scheme 2.

(Scheme 4). Catalytic reduction of the imine bond in **3** gave **9a**, which, without isolation, was converted into the isoindolinone **11a** by acetic acid.

It should be noted that, in the synthesis of isoindolinone derivatives **11** according to Scheme 3, the chirality present in the starting amino acid is retained in the product.

The reaction of **1a** with salicylaldehyde was disappointing as it did not give the expected product **12**, but a very insoluble polymeric material instead. However, the preformed Schiff's base **13** from salicylaldehyde and glycine gave, upon treatment with dicyclohexylamine (dca) and subsequent reaction with triethylborane, the boron heterocycle **14** (Scheme 5). Attempts to convert this dca-salt into the free acid failed; again an insoluble polymeric substance was obtained. In contrast, the salt **14** was readily transformed into the *p*-nitrobenzyl ester **15** on treatment with *p*-nitrobenzyl bromide. After reduction of the imine bond in **13**, reaction of **16** with triethylborane led smoothly to the boron complex **17**. Apparently, the imine bond in **12** prevents an intramolecular reaction of this kind. Probably, intermolecular reactions are favoured leading to the observed polymeric material.

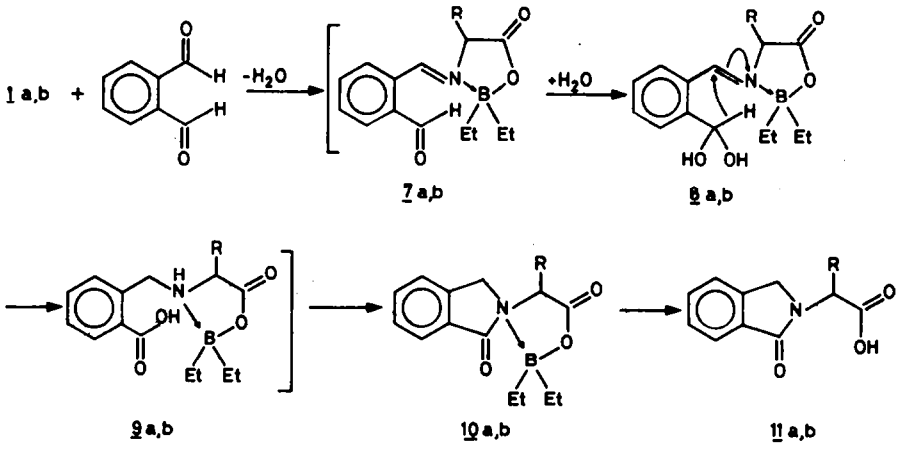
All compounds prepared were characterized by elemental analysis and spectra, and, where appropriate, by comparison with authentic samples (see Experimental section). Further investigation of the nucleophilic properties of the nitrogen atom in boroxazolidones is in progress.

EXPERIMENTAL

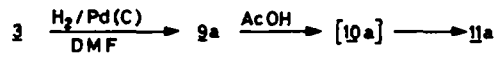
IR spectra were taken on a Perkin–Elmer 257 grating spectrometer. NMR spectra were recorded on a Varian EM 390 spectrometer using TMS as internal standard. All m.ps are uncorrected. Elemental analyses were performed in the Microanalytical Department of the University of Nijmegen.

N - *Benzylidene* - B,B - *diethylboroxazolidone* (**2a**). Freshly prepared[7] **1a** (0.01 mol) was suspended in benzene (100 ml). Benzaldehyde (1.04 ml, 0.01 mol) was added and the mixture was then heated at reflux employing a Dean–Stark water separator until no more water was produced. At that time the reaction mixture became homogeneous. The mixture was filtered with charcoal and the filtrate was concentrated. Addition of diisopropyl ether to the oily residue caused crystallization of product **2**. Recrystallization proved difficult, but the product was pure by NMR. NMR ($CDCl_3$): δ 0.3–1.0 (m, 10H, B–C_2H_5), 4.55 (d, 2H, CH_2CO), 7.6–7.9 (m, 5H, C_6H_5), 8.15 (t, 1H, CH=N).

N - (*o* - *Carboxybenzylidene*) - B,B - *diethylboroxazolidone* (**3**). To a freshly prepared solution of **1a** (0.1 mol) in dry



Scheme 3.



Scheme 4.

THF (100 ml) *o*-carboxybenzaldehyde (16 g, ~1 mol) was added. Then THF was removed *in vacuo* and benzene (150 ml) was added. This solvent was removed (with concomitant azeotropic distillation of water), affording a solid product (benzene operation was needed twice). The product was thoroughly washed with diisopropyl ether. Yield 90%, m.p. 160–162°. Recrystallization can be accomplished from acetic acid provided prolonged heating is avoided, as then deboration may occur. IR ν_{max} (KBr) 2940 (br), 1700, 1670 cm^{-1}; NMR (d_6-DMSO): δ 0.3–1.0 (m, 10H, B–C_2H_5), 4.4 (d, 2H, CH_2CO), 7.65–7.8 (m, 4H, C_6H_4), 8.9–9.0 (t, 1H, CH=N). (Found: C, 61.1; H, 6.5; N, 5.1. $C_{14}H_{18}BNO_4$ requires (M 275.093): C, 61.1; H, 6.6; N, 5.1%.)

N - [*o* - (*Methoxycarbonyl)benzylidene*] - B,B - *diethylboroxazolidone* (4). To a solution of 3 (0.01 mol) in dry dimethylformamide (50 ml) potassium t-butoxide (0.01 mol) was added. When the mixture became homogeneous, it was cooled to −20° and dimethyl sulfate (0.01 mol) was gradually added. The mixture was allowed to stand at room temp. overnight. After solvent removal water was added, giving a crystalline product, which was filtered off, washed with water, dried and recrystallized from toluene (or CCl_4). Yield 50%, m.p. 108–110°. IR ν_{max} (KBr) 1720 (br), 1662 cm^{-1}; NMR ($CDCl_3$): δ 0.4–1.0 (m, 10H, B–C_2H_5), 3.96 (s, 3H, OCH_3), 4.15 (d, 2H, CH_2CO), 7.4–7.8 and 8.1–8.2 (m, 4H, C_6H_4). (Found: C, 62.4; H, 6.8; N, 4.8. $C_{15}H_{20}BNO_4$ requires (M 289.118): C, 62.3; H, 7.0; N, 4.8%.)

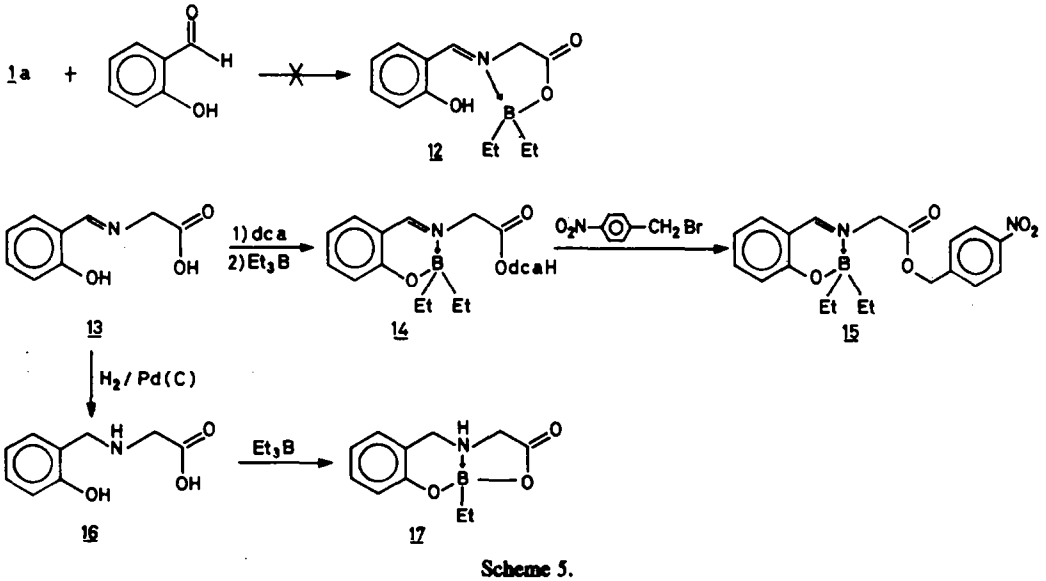
N-[*o*-(*p-Nitrophenoxycarbonyl)benzylidene*]-B,B-*diethylboroxazolidone*. To a cooled (0°) stirred suspension of 3 (0.01 mol) in dry THF (50 ml) was added *p*-nitrophenol (2.0 g) and dicyclohexylcarbodiimide (2.1 g). After stirring for 2 h at 0° and overnight at room temp. dicyclohexylurea was filtered off and washed with THF. The filtrate was then concentrated to dryness. The residue was washed with ether to remove excess of *p*-nitrophenol. The crude product was crystallized from acetonitrile. Yield 2.8 g (70%), m.p. 140–141°. IR ν_{max} (KBr) 1740, 1720 cm^{-1}; NMR (d_6-DMSO): δ 0.4–0.9 (m, 10H, B–C_2H_5), 4.31 (d, 2H, CH_2CO), 7.42–8.5 (m, 8H, arom. H), 8.94 (t, 1H, CH=N). (Found: C, 60.9; H, 5.3; N, 7.1. $C_{20}H_{21}BN_2O_6$ requires (M 396.185): C, 60.6; H, 5.3; N, 7.1%.)

Diethylboryl ester of 4-hydroxyisoquinoline-3-carboxylic acid (5). To a stirred solution of 4 (5 mmol) in dry dimethylformamide at −40° (10 ml) t-BuOK (5 mmol) was added. Stirring was continued until all butoxide had dissolved. The initial red color of the reaction mixture changed to yellow. The solution (20°) was then slowly poured into aqueous citric acid. Product 5 crystallized and was filtered off, washed with water and diisopropyl ether, dried, and finally recrystallized from CCl_4. Yield 75%, m.p. 150–151°. IR ν_{max} (KBr) 3280 (OH), 1670 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 0.6–0.8 (m, 10H, B–C_2H_5), 7.9–8.6 (m, 5H, C_6H_4 and –CH=N), 9.1–9.9 (br.s, 1H, OH). (Found: C, 65.4; H, 6.3; N, 5.4. $C_{14}H_{16}BNO_3$ requires (M 257.08): C, 65.4; H, 6.3; N, 5.4%.)

4-Hydroxyisoquinoline-3-carboxylic acid (6). *Method a.* Substance 5 (5.0 mmol) was dissolved in 1:1 acetic acid:conc. aqueous HCl (10 ml) by gentle heating. When the solution was homogeneous, the solvents were removed *in vacuo* leaving a solid. This was dissolved in ethanol–water (1:1) by heating and then neutralized with pyridine. On cooling the product 6 crystallized. Yield 80%, m.p. 218–220°. IR ν_{max} (KBr) 3515, 3460 (O–H), 1660 cm^{-1}; NMR (d_6-DMSO): δ 1.9 (s), 7.3 (m), 7.8 (m), 8.2 (s), peak ratio 1:2:2:1. (Found: C, 60.1; H, 4.0; N, 6.9. Calc for $C_{10}H_7NO_3 \cdot \frac{1}{2}H_2O$: C, 60.6; H, 4.1; N, 7.1%.)

Method b. Compound 5 (2.0 mmol) was dissolved in ethanol (10 ml) and 8-hydroxyquinoline (2.0 mmol) was added. The homogeneous reaction mixture was gently heated for 1 h, the resulting precipitate of 6 was filtered off and washed with ethanol and ether. Yield 300 mg (80%), m.p. 218–220°. IR ν_{max} (KBr) 3515, 1660 cm^{-1}; NMR: see above. (Found: C, 62.0; H, 3.6; N, 7.3. Calc for $C_{10}H_7NO_3$ (M 189.162): C, 63.5; H, 3.7; N, 7.4%.) Note that this product does not contain water of crystallization.

N-(*Carboxymethyl)isoindolinone* (11a). *From* 1a. To a solution of 1a (10 mmol) in acetonitrile (20 ml) an equimolar amount of *o*-phthalaldehyde was added. The mixture was refluxed for 3 h. The product precipitated and was collected, after cooling, by filtration. Yield 50%, m.p. 219–220° (lit.[9] 213–215°). IR ν_{max} (KBr) 2900 (br), 1745, 1720, 1640 cm^{-1}; NMR (d_6-DMSO): δ 4.26 (s, 2H,



Scheme 5.

C_6CH_2N), 4.5 (s, 2H, CH_2COOH), 7.4–7.7 (m, 4H, C_6H_4), 12.95 (br.s, 1H, COOH). (Found: C, 62.8; H, 4.7; N, 7.3. Calc for $C_{10}H_9NO_3$ (M 191.175): C, 62.8; H, 4.7; N, 7.3%.)

From **3**. A solution of **3** (10 mmol) in DMF (150 ml) with Pd/C (200 mg) was hydrogenated at atmospheric pressure. When the hydrogen uptake had ceased (approx. 1 h) the reaction mixture was filtered and concentrated *in vacuo*. The residue crystallized upon addition of diisopropyl ether (50 ml). The product was recrystallized twice from acetic acid. Yield 40%, m.p. 215–217°; this product was identical in all respects with that obtained from **1a**.

N - 1 - (1 - *Carboxy* - 2 - *phenylethyl)isoindolinone* (**11b**). This product was prepared from **1b** following the procedure described for **11a**. Yield 45%, m.p. 190°. IR ν_{max} (KBr) 1720, 1645 cm^{-1}; NMR (d_6-DMSO): δ 3.32 (two q, 2H, $PhCH_2$), 4.43 (s, 2H, C_6CH_2N), 5.2 (two d, 1H, CHCOOH), 7.1–7.8 (m, 9H, C_6H_5 and C_6H_4). (Found: C, 72.5; H, 5.4; N, 5.0. $C_{17}H_{15}NO_3$ requires (M 281.295): C, 72.6; H, 5.4; N, 5.0%.)

N-(*o-Hydroxybenzylidene)glycine* **13** (*dca salt*). Finely powdered glycine (0.1 mol) was suspended in MeOH (200 ml). Salicylaldehyde (0.1 mol) and dicyclohexylamine (0.1 mol) were added. After heating under reflux for 1 h the glycine had dissolved. On removal of the solvent the yellow dca salt of **13** was obtained in almost quantitative yield. NMR (d_6-DMSO): δ 1.0–2.1 (m, 22H), 2.9 (m, 2H), 4.31 (s, 2H, CH_2CO), 6.7–7.6 (m, 4H, C_6H_4), 8.27 (1H, CH=N).

The boron chelate **14**. The dca salt of **13** was heated and stirred with slightly more than 1 equiv. of Et_3B in THF until all solid material had dissolved (overnight). The solvent was removed *in vacuo* leaving a yellow crystalline product which was recrystallized from dimethyl formamide. Yield 90%, m.p. 175.5–177°. IR ν_{max} (KBr) 1640, 1655 cm^{-1}; NMR ($CDCl_3$): δ 0.4–2.3 (br.m, 30H), 3.0 (br.s, 2H, $N(CH)_2$), 4.17 (s, 2H, CH_2COOH), 6.7–7.4 (m, 4H, C_6H_4), 8.25 (s, 1H, CH=N).

Conversion of **14** *into the p-nitrobenzyl ester* **15**. The salt **14** (35 mmol) was dissolved in DMF (450 ml) with gentle heating at 80°. At this temperature *p*-nitrobenzyl bromide (35 mmol) was added. The mixture was kept at 80° for 0.5 h; dicyclohexylammonium bromide crystallized out. After cooling this salt was filtered off and the filtrate was concentrated *in vacuo*. The remaining oil was dissolved in AcOEt (200 ml) and then washed with water (4×) to remove the last traces of dicyclohexylammonium bromide. After drying ($MgSO_4$), removal of the solvent gave an oil which crystallized on standing. The product was recrystallized from acetonitrile. Yield 74%, m.p. 97–100°. IR ν_{max} (KBr) 1750, 1640, 1520, 1340 cm^{-1}; NMR ($CDCl_3$): δ 0.2–1.0 (m, 10H, $B-C_2H_5$), 4.2 (s, 2H, CH_2CO), 5.32 (s, 2H, CH_2O), 6.6–7.4 (m, 4H, C_6H_4O), 7.5 + 8.23 (ABq, 4H, J = 7.5 Hz, $C_6H_4NO_2$). (Found: C, 63.0; H, 6.1; N, 7.4. $C_{20}H_{23}N_2BO_5$ requires (M 382.20): C, 62.9; H, 6.1; N, 7.3%.)

N - (*o - Hydroxybenzyl)glycine* (**16**) *and its conversion into* **17**. To an aqueous solution of glycine (0.1 mol) 1 equiv. each of NaOH and salicylaldehyde were added. A yellow precipitate was formed which dissolved on standing and addition of some water. The homogeneous mixture was hydrogenated (Pd/C 10%) at 4–5 atm. After the uptake of 1 equiv. of hydrogen the mixture was filtered and acidified with acetic acid. On cooling to 0° the product crystallized. After washing with water it was recrystallized from acetic acid–water (1:1). Yield 70%, m.p. 215–217°. IR ν_{max} (KBr) 3060, 1640 cm^{-1}. The substance was too insoluble in DMSO and D_2O at room temperature for an NMR spectrum. (Found: C, 59.4; H, 6.1; N, 7.4. $C_9H_{11}NO_3$ requires (M 181.19): C, 59.7; H, 6.1; N, 7.7%.)

Product **16** (10 mmol) was added to a slight excess of Et_3B in THF (12 ml 1 M solution). The mixture was heated under gentle reflux and stirring until all solid had dissolved (overnight). After removal of the solvent white crystals were obtained which were recrystallized from acetic acid. Yield 60%, m.p. 210–211°. IR ν_{max} (KBr) 3260 (NH), 1720 cm^{-1}; NMR (d_6-DMSO): δ 0.25–1.05 (m, 5H, $B-C_2H_5$), 3.1–4.2 (m, 4H, CH_2CO and $C_6H_4CH_2N$), 8.0 (br.m, 1H, NH). (Found: C, 60.3; H, 6.3; N, 6.4. $C_{11}H_{14}BNO_3$ requires (M 219.033): C, 60.3; H, 6.4; N, 6.4%.)

REFERENCES AND NOTES

[1]These compounds are also named in the chemical literature as esters[2] or mixed anhydrides[3–5] of amino acids and di-alkyl (or aryl) borinic acid. We prefer the heterocyclic name[6] in accordance with Chemical Abstracts.

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