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Unexpected boratranes: BBr₃ mediated synthesis and mechanistic insights

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Abstract

Boratranes synthesis are predictably based on the reactions of triethanolamine derivatives with boric acid, or trialkyl borate and require prolonged heating of the reagents under reflux. Herein, the authors report an efficient synthesis of unexpected boratranes featuring on one hand three six-membered chelating ring or two six-membered and one five-membered chelating ring and on the other hand a trans-annular boron atom is bound to one nitrogen, two oxygen and one carbon atom. These novel boratranes have been synthetized by reacting N,N-bis(2-methoxybenzyl) alkynylamines with BBr₃ in dichloromethane at low temperature. The reaction mechanism was investigated by using density functional theory (DFT) calculations. A mechanistic pathway proceeding through a key dioxazaborocininium intermediate was proposed. This alternative protocol represents a convenient access to dissymmetric and functionalizable boratranes under mild conditions in good yields.

Keywords

Boratranes; Boron tribromide; Density functional calculations; O-demethylation.

1. Introduction

Atranes (Fig. 1) are specific tricyclic compounds displaying a trans-annular N-M dative bond involving a nitrogen atom at the bridgehead and an organoelement M (Si, B, C, Al, P...)[1,2] The presence of this intramolecular trans-annular M-N bond could justify their high thermodynamic stability and resistance to hydrolysis. Even though silatranes (M = Si) are the most studied,[3] different examples of boratranes (M=B) synthesis and characterisation revealed the interest of these compounds not only as theoretical objects, but also as valuable reagents,[4] materials,[5] as well as physiologically and pharmacologically active compounds[6] due to their unusual architecture. Some
studies of boratranes have been carried out on their stability,[7] their basicity,[8] and the substituents effects.[9] Until now, most of the reported boratran structures displayed three cycles with the same five- or six-membered rings size \((l = m = n = 1 \text{ or } 2)\) and with the boron atom bounded to three identical atoms \((X = Y = Z)\) such as oxygen, carbon or nitrogen. In 2011, was reported the first structurally-characterized boratran with two different ring sizes.[10]

![General chemical structure of atranes](image)

**Fig. 1.** General chemical structure of atranes

Classical methods for the synthesis of boratranes use boric acid[11] or trialkyl borate[12] as reagent in various organic solvents or without solvent. In most cases, the reactions require prolonged reaction time under reflux and removal of released water from the reaction mixture by distillation. We report here an access under mild conditions to such structures 1 and 2 (Fig. 2) by the unexpected reactivity of \(N, N\)-bis(2-methoxybenzyl) alkynylamines in O-demethylation of arylmethylether standard conditions, \(i.e.\) in the presence of an excess of boron tribromide.[16] These boratranes display unique structural features which are a boron atom binding to two atoms of different nature, \(i.e.\) O and C, and the presence of an intra-cyclic alkene double bond. Moreover, as their formation was not obvious, DFT calculations were performed in order to highlight a plausible reaction mechanism.

![Structures of boratranes 1 and 2.](image)

**Fig. 2.** Structures of boratranes 1 and 2.

2. **Results and Discussion**

The investigated boratranes 1 and 2 were prepared following the synthetic route represented in Scheme 1, starting from the secondary amine 3 readily prepared by reductive amination from 2-methoxybenzylamine and 2-methoxybenzaldehyde.[17] Compound 3 was initially alkylated with propargyl bromide at \(-78^\circ\text{C}\) in the presence NaH to give amine 4 in 69% yield according to a described procedure.[18] In an attempt to perform O-demethylation, derivative 4 was treated with excess of BBr\(_3\) in CH\(_2\)Cl\(_2\) at 0ºC. The expected diphenol was not obtained. However, a new compound 1 was isolated in 51.6% yield after tricky purification as the sole product. The \(^1\text{H}\) NMR spectrum of molecule 1 showed...
no signal corresponding to any protons from methoxy groups, the lack of the alkyne proton and the appearance of an intriguing signal at 5.98 ppm characteristic of an alkene proton. Moreover, the high-resolution mass spectrum of 1 indicated the presence of a product with a molecular formula C_{17}H_{15}BBrNO_{2}. These data, and in particular the presence of boron and bromine atoms, suggested the original tricyclic boratrane structure 1 shown in scheme 1. Crystallization of compound 1 in methanol allowed the isolation of high-quality crystals, from which an X-ray study confirmed the proposed structure (Fig. 3). We then envisioned to extend this result to the homolog alkyne amine 5, readily obtained by alkylation of derivative 3 with 4-bromobutylene in the presence of K_{2}CO_{3} and NaI in acetonitrile. Thus, treatment with an excess of BBr_{3} at 0°C gave similarly rise to compound 2 in 52.4% yield (Scheme 1). ^{1}H NMR data (alkene signal at 6.32 ppm) and high resolution mass spectroscopy (molecular formula : C_{18}H_{17}BBrNO_{2}) suggested a boratrane structure with three six-membered rings which was confirmed by single crystal X-ray diffraction analysis (Fig. 3).^{[19]}

**Scheme 1.** Synthesis of boratranes 1 and 2. Conditions and reagents: a) MeOH, RT, 12h then NaBH_{4}, RT, 6h (98%); b) For 4 (n=1): Propargylbromide, NaH, THF, RT (69%); For 5 (n=2): 4-bromobutylene, K_{2}CO_{3}, NaI, CH_{3}CN, reflux (81.6%). c) 10 equiv BBr_{3}, CH_{2}Cl_{2}, 0°C, 1h (51.6% for 1; 52.4% for 2).

**Fig. 3.** Molecular view of boratranes 1 (CCDC 2143122) and 2 (CCDC 2143123). Hydrogen atoms are not represented for the sale of clarity. Displacement ellipsoids are drawn at 50% probability.
The synthetized boratrane derivatives display mixed ring systems with boron atom linked to two oxygen atoms and one carbon atom. As shown in Fig. 3, the structure of 1 exhibits two similar six-membered rings adopting a boat conformation, a quasi-planar unsaturated five-membered one (the maximum deviation from the mean molecular plane is 0.051 Å), and a trans-annular B-N bond distance of 1.698(3) Å. The all six-membered rings of atrane 2 show half-chair conformations and the trans-annular B-N bond distance (1.636(2) Å) is among the shortest previously reported\[10\] (See supplementary data for selected crystallographic data).

Noteworthy, boratranes preparation using BBr\(_3\) as reagent is unprecedented. The formation mechanism of the unique structures of 1 and 2 which involves the reactivity of BBr\(_3\) towards methoxy groups and alkyne function\[20\] was investigated. As supplementary experiments, we showed that no reaction occurred starting from the corresponding diphenol analog of compound 4 under the same reaction conditions (10 equiv of BBr\(_3\), 0°C, 1h). Moreover, attempted reaction using only 1.1 equivalent of BBr\(_3\) (0°C, 1h) on compound 5 led to unreacted starting material. So, the presence of methoxy groups and an excess of BBr\(_3\) are required for the formation of boratranes derivatives.

We then explored the reaction mechanism of the formation of boratrane 1 from propargyl amine 4 by DFT computational calculations. Gaussian 09\[21\] was used for all computations using the DFT functional B3LYP\[22,23\] with the 6-31+G(d,p) basis set in combination with the dichloromethane continuum solvation model SMD (solvation model density) of Truhlar\[24\] to ensure consistency with experimental conditions. Analytical frequencies were calculated for all stationary points. The study of the reaction pathway was carried out by determining the stationary points and related enthalpies differences. All minima on the energy potential surface were characterized by frequency calculations, all of them being positive. All transition states exhibit a single negative frequency. For additional details, see “DFT calculations” in ESI.

DFT calculations were performed following the proposed mechanism pathway depicted in Scheme 2. The calculated relative enthalpies profile is shown on Fig.4. This computational investigation was built upon the Korich and Lord’s work\[25\] on the mechanism of BBr\(_3\) mediated demethylation of aryl methyl ethers by DFT calculations. We envisioned that after initial complexation of BBr\(_3\) with propargyl amine 4 to give the boro-ether adduct I (\(\Delta H = -14.9\) kcal/mol), a second molecule of BBr\(_3\) could abstract bromide to afford II and a BBr\(_4^-\) anion. The latter charged intermediates were computed to be thermodynamically favorable (\(\Delta H = -35\) kcal/mol). The subsequent formation of the key dioxazaborocinium intermediate III from II was slightly endergonic (+13.6 kcal/mol). BBr\(_4^-\) anion assisted demethylation of III proceeded through the transition state TS\(_a\) shifting the dynamic
equilibrium towards bromomethane and intermediate IV formation ($\Delta H = -38.1$ kcal/mol). The calculated $\text{TS}_a$ enthalpy value ($-13.8$ kcal/mol) correlates with the experimental reaction conditions which does not require any heating ($T = 0^\circ C$). As previously, $\text{BBr}_3$ could then abstract bromide from IV to afford V and a $\text{BBr}_4^-$ anion ($\Delta H = -52.8$ kcal/mol). A second thermodynamically favorable demethylation proceeded through transition state $\text{TS}_b$ ($-39.6$ kcal/mol) to afford intermediate VI and bromomethane ($\Delta H = -73.6$ kcal/mol). Finally, the presence of both species $\text{BBr}_4^-$/$\text{BBr}_3$ in equilibrium in the reacting mixture allowed the formation of the transition state $\text{TS}_c$ ($-62.3$ kcal/mol) leading to boratrane 1 ($\Delta H = -95.6$ kcal/mol) from intermediate VI. All the stationary points geometries and energies are described in the supplementary data.

As depicted in Fig. 4, both transition states $\text{TS}_a$ and $\text{TS}_b$ featured $\text{S}_\text{N}_2$-like geometries with a trigonal bipyramidal carbon center. The calculated C-O bond distance was found to be 1.932 Å and 1.997 Å, the C-Br bond distance 2.560 Å and 2.475 Å and the B-Br bond distance 2.109 Å and 2.120 Å for $\text{TS}_a$ and $\text{TS}_b$ respectively. Both transition states were characterized by a single negative frequency of $-415$ cm$^{-1}$ and $-405$ cm$^{-1}$ respectively for $\text{TS}_a$ and $\text{TS}_b$ vibrating in the direction of the created C-Br bond. In the last transition state $\text{TS}_c$ (Fig. 4), the boron atom and the alkenyl moiety got closer together (B-Calk distances were found to be 1.916 Å and 2.219 Å). Concomitantly, the nucleophilic $\text{BBr}_4^-$ anion attacked the boron-alkenyl complex leading to the C-Br bond formation (C-Br distance = 2.734 Å) and $\text{BBr}_3$ abstracted bromide from intermediate VI. In this final step, boratrane 1 was formed and $\text{BBr}_3$ molecule and $\text{BBr}_4^-$ anion were regenerated. The transition state $\text{TS}_c$ was characterized by a single negative frequency at $-138$ cm$^{-1}$ vibrating in the direction of the C-Br bond formation. An IRC (intrinsic reaction coordinates) calculation$^{[26]}$ was performed to both connect the transition state $\text{TS}_c$ with the boratrane 1 in the reverse direction and to intermediate VI in the forward direction on the potential energy surface (See figure S1 in supplementary data).
Scheme 2. Calculated pathway mechanism proposal for the formation of compound 1 from 4.
As visualized in Fig. 4, the computational proposed pathway for the formation of boratrane 1 from amine 4 in dichloromethane in the presence of an excess of BBr₃ is thermodynamically favored ($\Delta H = -95.6$ kcal/mol). This mechanistic proposal rationalizes the experimental reaction conditions (short time reaction and low temperature). A similar mechanism could be envisioned for the homologous formation of boratrane 2 from alkynylamine 5.

3. Conclusion
In conclusion, we described an efficient synthesis of original boratranes under mild conditions. Irrefutable proof for the structural identity of boratranes 1 and 2 was provided through NMR analysis and X-ray study. In addition, the experimental results were validated by means of a computational study, allowing a mechanistic rationalization. These results hence provide a significant contribution to the further development of boratranes chemistry.

4. Experimental Section

4.1. General information

All purchased chemicals were of the highest purity commercially available and used without further purification. Unless otherwise noted, all experiments were carried out under a nitrogen atmosphere. Solvents (CH$_2$Cl$_2$ and THF) were dried via a purification solvent system MB-SP-800 (MBRAUN). Melting points (mp) were obtained on a Buchi apparatus and are uncorrected. All reactions were monitored by TLC on silica gel Alugram® Xtra SIL G/UV254. Column chromatography was performed on Machery–Nagel silica gel. NMR spectra were recorded with Bruker Avance 300 instruments. Chemical shifts are given in ppm and are referenced by using the residual signals of the solvent as internal standard. Signals are described as follow: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS data were recorded on a Xero G2 QTOF (Waters) instrument.

4.2. N,N-bis-(2-methoxybenzyl)amine (3)

To a flask charged with 2-methoxybenzylamine (2.4 g, 17.5 mmol) dissolved in MeOH (29 mL, 0.5 M), was added 2-methoxybenzaldehyde (2 g, 14.7 mmol) dropwise. The resulting mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C and NaBH$_4$ (1.1 g, 29 mmol) was then added portion wise. After stirring for 6h at 0°C, cold water was then added to the mixture until gas evolution ceased. The aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated under vacuum to give the expected compound 1 as yellow oil (3.72 g, 98.5%). The crude product was directly used for the next step without any further purification. R$_f$ = 0.1 (PE/EtOAc = 8/2). $^1$H NMR (CDCl$_3$, 300 MHz) δ = 7.31–7.21 (m, 4H), 6.92 (td, $^3$J$_{HH}$ = 7.4 Hz, $^4$J$_{HH}$ = 1.1 Hz, 2 H), 6.86 (dd, $^3$J$_{HH}$ = 8.1 Hz, $^4$J$_{HH}$ = 1.1 Hz, 2H), 3.85–3.82 (m, 10H). The $^1$H NMR data are consistent with published data.$^{[27]}$

4.3. N,N-bis(2-methoxybenzyl)prop-2-yn-1-amine (4)

To a suspension of NaH (24 mg, 0.97 mmol) in dry THF (5 mL) at $-78$ °C under N$_2$, was added dropwise a solution of amine 1 (193 mg, 0.75 mmol) in THF (7mL). The mixture was warmed to room temperature and stirred for 2 h. After cooling to 0°C, propargyl bromide (0.1 mL, 0.97 mmol) was added dropwise to the reaction mixture. After stirring overnight at rt, the yellowish solution was
quenched with brine (7 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. Purification by silica gel column chromatography (PE / EtOAc= 9:1) afforded the pure compound 4 as a colorless oil (152 mg; 69% yield). R₁ = 0.5 (PE/EtOAc = 4/1). ¹H NMR (300 MHz, CDCl₃) : δ = 7.58 (dd, ³J_H,H=7.5, ⁴J_H,H=1.8 Hz, 2H); 7.27 (td, ³J_H,H= 7.8 Hz, ⁴J_H,H=1.8 Hz, 2H); 7.00 (td, ³J_H,H= 7.5 Hz, ⁴J_H,H=1.1 Hz, 2H); 6.90 (d_app, ³J_H,H=7.8 Hz, 2H); 3.85 (s, 6H, CH₃); 3.84 (s, 4H); 3.43 (d, ³J_H,H=2.4 Hz, 2H); 2.34 (t, ³J_H,H=2.4 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ = 157.8; 130.2; 127.0; 120.2; 110.3; 79.5; 72.9; 55.3; 51.4; 42.0. HRMS (DCI/CH₃CN): m/z calcd for C₁₉H₂₂NO₂ : 296.1651 [M+H]^+; found: 296.1652.

4.4. N,N-bis(2-methoxybenzyl)but-2-yn-1-amine (5)

4-Bromobutyne (0.36 mL, 4 mmol) was added to a mixture of amine 1 (516 mg, 2mmol), NaI (149 mg, 1 mmol) and K₂CO₃ (829 mg, 6 mmol) in CH₃CN (25mL). The reaction mixture was heated under reflux for 12 h. After cooling to room temperature, the solid was filtered off. The filtrate was concentrated under vacuum and the residue was dissolved in CH₂Cl₂. The resulting solution was washed with 5% aqueous NaOH solution, brine, dried over Na₂SO₄, and concentrated under vacuum to give pure compound 5 as a yellow oil (612 mg, 99%). R₁ = 0.5 (EP/EtOAc = 4/1). ¹H NMR (300 MHz, CDCl₃) : δ = 7.61 (dd, ³J_H,H= 7.4 Hz, ⁴J_H,H=1.8 Hz, 2H); 7.25 (td, ³J_H,H= 7.8 Hz, ⁴J_H,H=1.8 Hz, 2H); 6.99 (td, ³J_H,H=7.4 Hz, ⁴J_H,H=1.1 Hz, 2H); 6.89 (dd, ³J_H,H=8.3 Hz, ⁴J_H,H=1.1 Hz, 2H); 3.85 (s, 6H); 3.77 (s, 4H); 3.43 (d, ³J_H,H=2.4 Hz, 2H); 1.98 (t, ³J_H,H=2.7 Hz). ¹³C NMR (CDCl₃, 75 MHz): δ = 157.5; 129.9; 127.8; 127.7; 120.5; 110.2; 83.5; 68.8; 55.3; 52.8; 51.7; 17.0. HRMS (DCI/CH₃CN) : m/z calcd for C₂₀H₂₄NO₂ : 310.1807 [M+H]^+; found: 310.1799.

4.5. General procedure for the synthesis of compounds 1 and 2

BBr₃ (1M in Hexane, 10 equiv) was added dropwise to an ice-cooled solution of alkyne (1 equiv) in anhydrous CH₂Cl₂ (0.025 M) under nitrogen. The resulting reaction mixture was stirred at 0°C for 1h, before quenching by careful addition of water (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give yellow solid which was then triturated in a minimum of EtOH and filtered off to give pure white solid.

4.5.1 16-Bromo-12H,14H-6i,4,13i₄-6,13-prop[1]enobenzo[e]benzo[5,6][1,3,2]oxazaborinino[2,3-b][1,3,2]oxazaborinine (1)

Following the general procedure starting with 4 (150 mg, 0.51 mmol), compound 1 was obtained as a white crystal solid (93 mg, 51.6%). m.p. > 220°C. ¹H NMR (DMSO-d₆, 300MHz) : δ = 7.25 (dd, ³J_H,H= 7.6, ⁴J_H,H= 1.6Hz, 2H); 7.23-7.20 (m, 2H); 6.88 (td, ³J_H,H= 7.4, ⁴J_H,H= 1.2Hz, 2H); 6.94 (d_app, ³J_H,H= 7.9, 2H);
5.98 (t, \(^4J_{HH}= 1.9\)Hz, 1H); 4.18 (d, \(^6J_{HH}= 13.2\)Hz, 2H); 4.05 (d, \(^8J_{HH}= 13.1\)Hz, 2H); 3.85 (d, \(^4J_{HH}= 1.9\)Hz, 2H). \(^{13}\)C NMR (DMSO-\(d_6\), 75 MHz): \(\delta = 156.2; 136.3; 130.2; 128.6; 122.4; 120.4; 118.4; 68.9; 57.0\). HRMS (DCI/CH\(_4\)) : m/z calcd for C\(_{17}\)H\(_{16}\)BBrNO\(_2\) : 356.0457 [M+H]+; found: 356.0453.

4.5.2 17-Bromo-12H,14H-6\(\alpha,4\),13\(\alpha\)-6,13-butenbenzo[\(e\)]benzo[5,6][1,3,2]oxazaborinino[2,3-b][1,3,2]oxazaborinine (2)

Following the general procedure starting with 5 (200 mg, 0.65 mmol), compound 2 was obtained as a white crystal solid (125 mg, 52.4%). m.p. > 220°C. \(^1\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta = 7.21 (ddd, ^3J_{HH}=8.3\) Hz, \(^5J_{HH}=7.2\) Hz, \(^4J_{HH}=1.8\) Hz, 2H); 6.93 (ddd, \(^5J_{HH}= 7.4\) Hz, \(^3J_{HH}=6.2\) Hz, \(^4J_{HH}=1.5\) Hz, 4H); 6.83 (td, \(^5J_{HH}=7.3\) Hz, \(^4J_{HH}=1.2\) Hz, 2H); 6.32 (t, \(^4J_{HH}=1.5\) Hz, 1H); 4.15 (m, 4H); 3.28 (t, \(^5J_{HH}=6.3\) Hz, 2H); 2.91 (td, \(^5J_{HH}=6.4\) Hz, \(^4J_{HH}=1.6\) Hz, 2H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta = 151.9; 137.8; 129.9; 127.1; 121.9; 119.8; 119.4; 115.2; 55.8; 52.7; 34.2\). HRMS (DCI/CH\(_4\)) : m/z calcd for C\(_{18}\)H\(_{18}\)BBrNO\(_2\) : 370.0614 [M+H]+; found: 370.0608.

4.6. Computational methods

Gaussian 09\(^{[21]}\) was used for all computations using the DFT functional B3LYP with the 6-31+G(d,p) basis set in combination with the dichloromethane continuum solvation model SMD (solvation model density). Analytical frequencies were calculated for all stationary points. The study of the reaction pathway was carried out by determining the stationary points and related enthalpies differences. All minima on the energy potential surface were characterized by frequency calculations, all of them being positive. All transition states exhibit a single negative frequency.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

The following is the Supplementary data to this article :

References and notes

[19] Under the same reaction conditions (excess BBr$_3$, CH$_2$Cl$_2$, 0°C) the homologous alkyne (n = 3) led to a complex unusable mixture.