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Preparation of *N,N,N′,N′*-tetramethylethylenediamine adducts of new monosubstituted boranes

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Abstract

TMED · $2BH_2CN$ (where TMED = *N,N,N′,N′*-tetramethylethylenediamine) was prepared more effectively by the use of a methylsulphide solution of the oligomer $(BH_2CN)_n$ compared to previous procedures. When ethylated with Et_3OBF_4, TMED · $2BH_2CN$ was transformed into [TMED · $2BH_2CNEt$][BF_4]$_2$, which can be regarded as a cationic boron compound containing an ethylisonitrile ligand. In aqueous medium the [TMED · $2BH_2CNEt$]$^{2+}$ ion (nitrilium ion) slowly hydrolyses, but it forms precipitates with large nonreactive anions (such as PF_6^- and BPh_4^-). At elevated temperatures, the nitrilium ion was converted more rapidly and in higher yields than in the previous procedures, to TMED · $2BH_2COOH$, from which TMED · BH_2COOH can then be prepared. Anionic reactants undergo nucleophilic addition or cycloaddition reactions with the nitrilium ion, giving good yields of the new complexes TMED · $2BH_2X$ (where X = *N*-ethylthiocarbamoyl, *N*-ethyliminocyanomethyl and 5-(1-ethyl)tetrazolyl group).

Introduction

The amine-carboxyboranes ($R_3N \cdot BH_2COOH$) and their derivatives can be regarded as being isoelectronic and isosteric boron analogues of the α-amino acids, protonated glycine and dipolar betaine ($H_3N^+–CH_2COOH$ and $Me_3N^+–CH_2$-COOH) [1–4]; they possess considerable anti-tumor [5], anti-inflammantory [6] and antihyperlipidemic [7] activity.

In view of the potential biological activity, we set out to prepare these amine complexes of new monosubstituted boranes.

Results and discussion

The amine-cyanoboranes are used as the starting materials for the synthesis of the amine-carboxyboranes and their derivatives. They can be prepared by the

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reaction of amine-halogenoboranes with alkaline metal cyanides [8,9], amine-boranes with mercury(II) cyanide [10] in addition to $NaBH_3CN$ with amines or amine hydrochlorides via the BH_2CN species, synthesized in situ [11–13]. The most effective procedure is the use of a methylsulphide solution of the $(BH_2CN)_n$ oligomer [14]. Its applicability was clearly shown in the synthesis of TMED · $2BH_2CN$ (where TMED = *N,N,N′,N′*-tetramethylethylenediamine) (eq. 1).

$$\text{TMED} + \frac{2}{n}(BH_2CN)_n \xrightarrow{Me_2S} \text{TMED} \cdot 2BH_2CN \qquad (1)$$

The product was isolated after 1 h in 95% yield, while the previous method [11] gave an 88% yield only after 100 h.

The ethylation of amine-cyanoboranes with Et_3OBF_4 leads to cationic boron compounds of nitrilium ion type ($[A \cdot BH_2CNEt]^+$), which have previously not been isolated [1–3,15–21]. In the case of TMED · $2BH_2CN$ we found that it was not necessary to use the large excess of the ethylating agent given in the literature [1–3,15–21]. When the Et_3OBF_4 excess was varied in the range of 0–150%, there was no change in the yield of the $[TMED \cdot 2BH_2CNEt][BF_4]_2$ (nitrilium salt) (eq. 2).

$$\text{TMED} \cdot 2BH_2CN + 2\ Et_3OBF_4 \xrightarrow[\text{reflux}]{CH_2Cl_2} [\text{TMED} \cdot 2BH_2CNEt][BF_4]_2 \qquad (2)$$

After refluxing for 6 h, the crystalline nitrilium salt was obtained in a yield of 93%. The product was purified by recrystallization from acetonitrile. It is soluble in polar solvents (e.g. water, DMF and DMSO), but undergoes slow hydrolysis in aqueous medium at room temperature. The rate of the hydrolysis is sufficiently low for the nitrilium ion to be precipitated with large, unreactive anions in unchanged form (eq. 3).

$$[\text{TMED} \cdot 2BH_2CNEt]^{2+} + 2\ X^- \xrightarrow{H_2O} [\text{TMED} \cdot 2BH_2CNEt][X]_2 \qquad (3)$$

When $X^- = PF_6^-$ and BPh_4^-, the yields are 85 and 64%, respectively.

The IR spectrum of the nitrilium ion (see Experimental section and Table 1) shows that the ion can be regarded as a cationic boron compound containing the ligands TMED and ethylisonitrile. The two ν(B–H) vibration bands are found in the range 2600–2380 cm^{-1} and are characteristic of cationic boron compounds [22]. From a comparison of the ν(C≡N) frequencies for the isonitrile complexes of the transition metals and the boron it was stated (see Table 1) that the isonitrile group in the nitrilium ion has the highest ν(C≡N) frequency recorded up to now [23–26]. Since there is no possibility for back-donation from the boron atom to the isonitrile group in the nitrilium ion, the bond order increases in the coordinated isonitrile group which leads to a considerable increase in the wavenumber of the ν(C≡N) band [26].

It is known from the literature that prepared, but not isolated, $[TMED \cdot 2BH_2CNEt][BF_4]_2$ hydrolyses rapidly in alkaline medium to give a good yield of TMED · $BH_2C(O)NHEt$, while in acidic medium it is hydrolysed during 72 h to TMED · $2BH_2COOH$, which can be prepared in a yield of 60% [2]. When pure nitrilium salt was refluxed in water for 5 min, we found that it gave the TMED · $2BH_2COOH$ in a much better yield (85%).

Table 1

ν(C≡N) data of some of the isonitriles and isonitrile complexes of transition metals and of boron

Compound	ν(C≡N) (cm^{-1})	Ref.
MeNC	2142	24
$(MeNC)Fe(CO)_4$	2213	24
$(MeNC)BMe_3$	2247	23,26
EtNC	2148	26
$[Mn(EtNC)_6][PF_6]_2$	2208	26
$[TMED \cdot 2BH_2CNEt][BF_4]_2$	2311	
$[TMED \cdot 2BH_2CNEt][PF_6]_2$	2309	
$[TMED \cdot 2BH_2CNEt][BPh_4]_2$	2304	
i-PrNC	2140	26
$(i\text{-}PrNC)BPh_3$	2265	23,26
t-BuNC	2143	26
cis-$PdCl_2(CN\text{-}t\text{-}Bu)_2$	2251	25

Base exchange can be used for the preparation of amine-carboxyboranes and their derivatives (eq. 4) [3,15,17–19], which is similar to the synthesis of amine-cyanoboranes [8,21].

$$A \cdot BH_2COOH + A' \rightarrow A' \cdot BH_2COOH + A \quad (4)$$

(A, A′ = amine, phosphine)

When A and A′ were TMED, the new non-symmetrical monocarboxyborane adduct $TMED \cdot BH_2COOH$ was obtained in 77% yield in an acetonitrile medium. In contrast with $TMED \cdot 2BH_2COOH$, the resulting crystalline material is soluble both in water and in organic solvents. The IR spectrum of the compound reveals that it contains hydrogen bonds, but the two ν(COO) bands characteristic of the deprotonated carboxyl group were not present.

The nitrilium ion reacts with anionic reagents even under mild conditions. A nucleophilic addition reaction occurs at the carbon atom of the isonitrile group (eq. 5) which is sometimes followed by an intramolecular rearrangement (eqs. 6, 7).

$$[TMED \cdot 2BH_2CNEt]^{2+} + 2\,X^- \rightarrow TMED \cdot 2BH_2\text{–}C(X)=N\text{–}Et \quad (5)$$

($X^- = CN^-, SH^-, N_3^-$)

The nitrilium ion reacts rapidly with the cyanide ion in aqueous medium. The product formed separates out and can be isolated in 95% yield. The IR spectrum shows that the product is a new compound and not an ion-pair. The ν(C≡N) band, characteristic of the nitrilium ion, was found to have disappeared, and new vibrations, ν(C≡N) and ν(C=N), appeared at 2191 and 1590 cm^{-1}, respectively.

In aqueous medium SH^- ion reacts with nitrilium ion and the resulting *N*-ethyl-thiocarbamoylborane complex separates out (eq. 6).

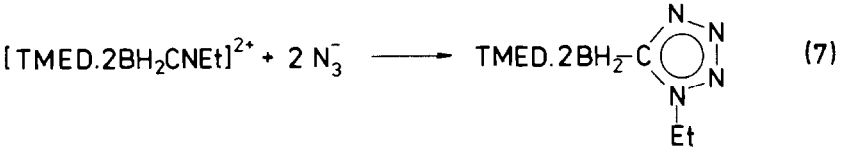
$$[TMED \cdot 2BH_2CNEt]^{2+} + 2\,SH^- \rightarrow TMED \cdot 2BH_2\text{–}C(S)\text{–}NHEt \quad (6)$$

The product was prepared in a yield of 90%. If the NaSH solution used was not saturated with H_2S, a large proportion of the nitrilium ion converted in a fast

side-reaction into TMED · $2BH_2C(O)NHEt$ which was isolated in a yield of 91%. The *N*-ethylthiocarbamoylborane complex is stable only in the solid state, below −25 °C. In solution (e.g. in acetonitrile) it undergoes slow decomposition even at −25 °C. At room temperature, the decomposition half-life of the dissolved material is approximately 1 day.

Attempts to prepare TMED · $2BH_2C(S)NHEt$ in non-aqueous media were unsuccessful.

In dimethylformamide the nitrilium ion undergoes cycloaddition with azide ion and *N,N,N′,N′*-tetramethylethylenediamine-bis(5-(1-ethyl)tetrazolylborane) is formed (eq. 7), in 68% yield.



(7)

The product is very stable when solid. It can be recrystallized from acetonitrile.

It is noteworthy that a number of tetrazole derivatives show appreciable biological activity [27], while the 5-substituted tetrazolyl group can be regarded as an analogue of the carboxyl group on the basis of its biological activity [28].

The results obtained show that the pure compounds contained an amine-ethyliso-nitriledihydroboron(III) cation which will be useful intermediates for the synthesis of new amine-monosubstituted borane complexes.

A study of the biological activities of the new compounds is in progress.

Experimental

With the exception of the reactions performed in aqueous medium, the experiments were carried out by use of Schlenk techniques [29] in dry, oxygen-free nitrogen atmosphere. The solvents used were also free of water and oxygen. The $NaBH_3CN$ (Aldrich) was purified by recrystallization from a mixture of THF and CH_2Cl_2. Et_3OBF_4 was prepared by use of the method by Meerwein [30]. A methylsulphide solution of $(BH_2CN)_n$ oligomer was prepared by use of the method by Győri et al. [14]. The boron contents of the compounds were determined by acid-base titration in the presence of mannitol after fusion with NaOH. The IR, ^1H and ^{11}B NMR spectra were recorded on Perkin–Elmer 283 B and Bruker WP 200 SY instruments. The NMR and IR data are given in ppm and cm^{-1}, respectively. The internal standards for the ^1H and ^{11}B NMR spectra were TMS and $Et_2O \cdot BF_3$, respectively. The abbreviations used are as follows: sg: singlet, d: doublet, t: triplet, q: quartet, sx: sextet, w: weak, m: medium, s: strong, v: very, sp: sharp, br: broad, sh: shoulder, $C_3H_5N_4$: 5-(1-ethyl)tetrazolyl.

Preparation of TMED · $2BH_2CN$

A 2.38 *M* solution of $(BH_2CN)_n$ oligomer in methyl sulphide (30.0 ml, 71.4 mmol) was added dropwise to a methyl sulphide solution (20 ml) of TMED (4.15 g, 35.8 mmol) at a rate such that the solution did not boil. After stirring for 30 min, the precipitate formed was filtered off, washed with methylsulphide (3 × 20 ml) and dried. The product was a white, crystalline substance (6.58 g, 33.9 mmol, 95%).

Anal. Found: B, 11.23 (calc: 11.15%); ^{1}H NMR (DMSO) δ: 2.68(sg,12H,NMe_2), 3.23(sg,4H,N–CH_2–); ^{11}B NMR (DMSO) δ: −15.2; IR (KBr): 2467m (ν(B–H)), 2329w,br (ν(B–H)), 2191w,sp (ν(C≡N)); m.p. 170–171°C.

Preparation of [TMED · 2BH_2CNEt][BF_4]$_2$

To a solution of 5.92 g (30.5 mmol) of TMED · 2BH_2CN in 100 ml methylene chloride was added 40 ml of a solution of Et_3OBF_4 (13.86 g, 72.9 mmol) in methylene chloride. The reaction mixture was refluxed for 6 h and then cooled to room temperature. The resulting crystals were filtered off, washed with methylene chloride (3 × 30 ml) then with ether (3 × 30 ml), and finally dried, to give the white non-hygroscopic crystals (11.96 g, 28.4 mmol, 93%). Anal. Found: B, 10.10 (calc: 10.16%); ^{1}H NMR (D_2O) δ: 1.52(t,6H,CH_3–CH_2–), 2.89(sg,12H,NMe_2), 3.44(sg,4H,N–CH_2–), 4.09(q,4H,CH_3–CH_2–); ^{11}B NMR (DMSO) δ: −1.0(nitrilium ion), −15.2(BF_4^-); IR (KBr): 2467m (ν(B–H)), 2434m (ν(B–H)), 2311m,sp (ν(C≡N)), 1058vs,br (ν(B–F)); m.p. 88–89°C (decomp.).

Preparation of [TMED · 2BH_2CNEt][PF_6]$_2$

To a solution of 0.663 g (1.56 mmol) [TMED · 2BH_2CNEt][BF_4]$_2$ in 10 ml water was added 15 ml of KPF_6 solution (0.674 g, 3.66 mmol). The resulting precipitate was filtered off, washed with water (2 × 10 ml), and dried in a current of air for 5 min. The partially dried material was washed with ether (3 × 10 ml) and finally dried to constant weight in nitrogen. The product was a white powder (0.727 g, 1.34 mmol, 85%). Anal. Found: B, 4.03 (calc: 3.99%); ^{11}B NMR (DMSO) δ: −0.9; IR (KBr): 2466w (ν(B–H)), 2429w (ν(B–H)), 2309w,sp (ν(C≡N)), 832vs,br (ν(P–F)); m.p. 167–168°C (decomp.).

Preparation of [TMED · 2BH_2CNEt][BPh_4]$_2$

The product was obtained from 0.266 g (0.53 mmol) nitrilium salt and 0.548 g (1.60 mmol) $NaBPh_4$, by the procedure described for [TMED · 2BH_2CNEt][PF_6]$_2$, as a white powder (0.304 g, 0.34 mmol, 64%). Anal. Found: B, 4.79 (calc: 4.86%); ^{11}B NMR (DMSO) δ: −6.8(nitrilium ion), −8.0(br, BPh_4^-); IR (KBr): 2467w,br (ν(B–H)), 2425w,br (ν(B–H)), 2304w,sp (ν(C≡N)); m.p. 80–81°C (decomp.).

Preparation of TMED · 2BH_2C(S)NHEt

To a vigorously stirred 0.248 *M* aqueous solution of NaHS (11.65 ml, 2.88 mmol) saturated with H_2S was added 0.615 g (1.44 mmol) of [TMED · 2BH_2CNEt][BF_4]$_2$ in small portions. Stirring of the reaction mixture was continued for 10 min after the addition, and the resulting precipitate was then filtered off, washed with water (2 × 5 ml), and dried to constant weight in a stream of nitrogen. The product was a white powder (0.415 g, 1.29 mmol), the yield is 90%. It was stored in a nitrogen atmosphere at a temperature below −25°C. Anal. Found: B, 6.74 (calc: 6.80%); ^{1}H NMR ($CDCl_3$) δ: 1.26(t,6H,CH_3–(CH_2–)), 2.81(sg,12H,NMe_2), 3.72(sx,4H,–CH_2–(CH_3)), 3.96(sg,4H,–CH_2–N), 7.65(sg,2H,NH); ^{11}B NMR (CH_3CN/DMSO) δ: −2.6; IR (KBr): 3360s,sp (ν(N–H)), 2380m,br (ν(B–H)), 2338m,sh (ν(B–H)), (2380sh, 2310sh), 1508vs,sp (ν(C=S)).

Preparation of TMED · 2BH_2C(CN)=NEt

The procedure described for TMED · 2BH_2C(S)NHEt was used to prepare the product, which was obtained from [TMED · 2BH_2CNEt][BF_4]$_2$ (4.12 g, 9.69 mmol)

and an aqueous solution (30 ml) of NaCN (1.20 g, 24.5 mmol), a white powder (2.80 g, 9.34 mmol, 96%). Anal. Found: B, 7.20 (calc: 7.11%); ^{1}H NMR ($CDCl_3$) δ: 1.24(t,6H,CH_3–(CH_2–)), 2.69(sg,12H,NMe_2), 3.41(sg,4H,N–CH_2–), 3.72(q,4H,–CH_2–(CH_3)); ^{11}B NMR (CH_3CN) δ: −6.7; IR (KBr): 2363vs,br (ν(B–H)), 2191vw,sp (ν(C≡N)), 1590m,br (ν(C=N)).

Preparation of TMED · 2BH$_2$–C$_3$H$_5$N$_4$

To a suspension of 1.706 g (26.3 mmol) NaN_3 in 8 ml DMF was added dropwise 30 ml of a solution of [TMED · $2BH_2CNEt$][BF_4]$_2$ (5.53 g, 13.0 mmol) in DMF, a rate such that the temperature did not rise above 30 °C. The reaction mixture was stirred for 10 min after addition of the solution. The resulting precipitate was filtered off, washed with DMF (10 ml), and then with ether (3 × 10 ml) and dried in a stream of nitrogen. The product was a white powder (2.95 g, 8.87 mmol, 68%). Anal. Found: B, 6.39 (calc: 6.43%); ^{1}H NMR ($CDCl_3$) δ: 1.45(t,6H,CH_3–(CH_2–)), 2.82(sg,12H,NMe_2), 3.80(sg,4H,–CH_2–N), 4.30(q,4H,–CH_2–(CH_3)); ^{11}B NMR (CH_3CN) δ: −10.1; IR (KBr): 2373s,br, ν(B–H)), (2403sh, 2330sh, 2298sh), 1481m,sp, 1378s,sp, 1186s,sp, 1147s,sp, 1112s,sp, 1089s,sp; m.p. 144–145 °C.

Preparation of TMED · 2BH$_2$COOH

A suspension of 1.23 g (2.91 mmol) [TMED · $2BH_2CNEt$][BF_4]$_2$ in 8 ml water, was boiled for 5 min and then cooled to room temperature. The resulting solid material was filtered off, washed with water (3 × 5 ml), and dried in a current of air. The product was a white crystalline substance (0.57 g, 2.46 mmol, 85%). Anal. Found: B, 9.27 (calc: 9.32%); ^{1}H NMR (D_2O) δ: 2.70(sg,12H,NMe_2), 3.35(sg,4H, –CH_2–N); ^{11}B NMR (DMSO) δ: −10.5; IR (KBr): 2715m,br (ν(O–H,assoc.)), 2630w,br (ν(O–H,assoc.)), 2565w,br (ν(O–H),assoc.)), 2414m,br (ν(B–H)), 1643s,br (ν(C=O)); m.p. 270 °C (decomp.).

Preparation of TMED · BH$_2$COOH

To a suspension of 0.38 g (1.65 mmol) of TMED · $2BH_2COOH$ in 10 ml acetonitrile was added 1.0 ml (0.77 g, 6.63 mmol) TMED. The reaction mixture was refluxed for 1 h. The resulting clear solution was evaporated to dryness at reduced pressure. Ether (10 ml) was added to the residue and the undissolved material was filtered off, washed with ether (3 ml) and dried in a stream of nitrogen. The crude product (0.486 g) was extracted into ether and the extract was cooled to −20 °C. The resulting crystals were filtered off, washed with ether cooled to −20 °C (3 ml) and finally dried in a stream of nitrogen to give white crystals (0.44 g, 2.53 mmol, 77%). Anal. Found: B, 6.20 (calc: 6.21%); ^{1}H NMR δ: 2.64(sg,6H,NMe_2), 2.70(sg,6H,N′Me_2), 3.20(d,2H,–CH_2–N), 3.28(d,2H,–CH_2–N′); ^{11}B NMR (CH_3CN) δ: −10.1; IR (KBr): 2688w,br (ν(O–H,assoc.)), 2567w,br (ν(O–H,assoc.)), 2372s,br (ν(B–H)), 1950vw,vbr (ν(N–H,assoc.)), 1652s,br (ν(C=O)); m.p. 101–102 °C.

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