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SOME AMIDE FORMING REACTIONS INVOLVING BORON REAGENTS

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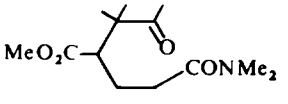
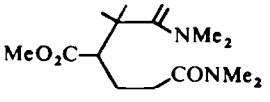
Abstract—Attempts to evolve a new peptide synthesis using boron reagents have led to several new amide syntheses, involving either trialkylboranes, trialkoxyboranes, chlorodialkoxyboranes or dialkoxyboranes. The method using the readily available trimethoxyborane may be of general synthetic value. A new peptide synthesis was realized that gave a product of high optical purity but the low conversions achieved do not make this approach of value, in practise.

WE HAVE previously shown that aminoboranes are reactive entities with certain organic functional groups,[1,2] in particular converting ketones to enamines, β-keto-esters to enamine amides, β-diketones to β-enaminoketones and carboxylic acids to amides. Certain analogies exist with the trisdialkylaminophosphines,[3] although different utilization of the amine groups points to different mechanisms. Subsequent investigations[4a,d] have shown that tetrakisdimethylaminotitanium is a highly efficient reagent for the production of enamines, but reacts vigorously with carboxylic acids, esters and amides to give 1,1,1-triamines and vinyledene*bis*dimethylamines.[4b] Trisdialkylaminoarsines[4a,5] may also yield either 1,1-diaminals or enamines from ketones and aldehydes. Trimethyltindimethyl amide produces amides from carboxylic esters and, very unusually, yields β-ketoamides from β-keto-esters.[6]

The use of metal halide and amine has been found[4c] to be an efficient method for the production of enamines. In this case the active reagent may well *not* be the simply derived metal amides, as sometimes the result may differ from that found using the metal amide. Thus with $Ti(NMe_2)_4$, compound I gave an irresolvable mixture of compounds with complete loss of optical activity due to the great reactivity of the reagent. With titanium chloride and dimethylamine, however, compound II was isolated with high optical integrity.[7]



I



II

The original mechanism postulated for the reaction of trisdialkylaminoboranes with carboxylic acids is as shown in Eq. 1

The scheme is one of many examined in more detail in a later paper. All the schemes postulate salt formation followed by production of the mixed anhydrides (III). The initial protonation is reasonable as even with compounds containing only one B-N

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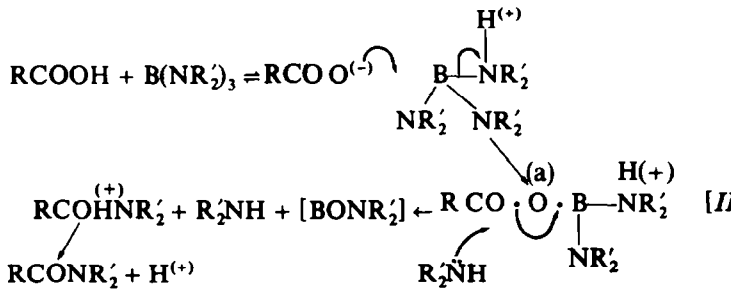

(1)

bond the well-known back donation *via* the π-system is balanced by charge transfer from boron to nitrogen through the σ-system.[8,9] With three amino groups attached to the one boron atom, protonation should be facile. Once this has occurred nucleophilic attack by the carboxylate group would lead to expulsion of an amine and production of III.

The mild conditions selectivity and high yields make the amide producing reaction of aminoboranes a useful synthetic reaction of aminoboranes, the often troublesome preparation of acid chloride being avoided. The method suffers from the disadvantage that only one-third of the amine groups are utilised, and also that a strong nucleophile (amine) is liberated during the reaction.

However, the "activated ester" (III) is merely one example of the general case, $R \cdot CO_2BXY$ (IV), which, if produced, should be capable of reaction with many nucleophiles. In particular a new peptide synthesis using intermediates of type IV seemed possible.

Trioctylborane (V) is readily available[10] and it is known that cleavage of the alkyl groups by carboxylic acids is ready, stepwise[11,12] and virtually specific for carboxylic acids. The products are said to be $[RCO_2]_nBR_{3-n}$. The equilibration of di-n-butylacetoxyborane by route (2) is known however.[13]

$$2MeCO_2B \cdot {}^nBu_2 \rightleftharpoons ({}^nBu^2B)_2O + (MeCO)_2O \quad (2)$$

The reaction of caproic acid and V (1 : 1) was very slow at −20° and addition of butyl amine, whilst giving neither amide nor carboxylate salts, produced an uncharacterized species sufficiently stable to survive unchanged on heating the mixture for 6 hr at 65°. Prolonged heating at 138°, however, gave the desired amide in 90–93% yield.

When the addition of acid was carried out at room temperature an acyloxyborane (ν_{max}^{CO} 1619 cm^{-1})[13] was produced, without any anyhydride formation. This product reacted rapidly with n-butyl amine to give a species (ν_{max}^{CO} 1660 cm^{-1}) which though rapidly hydrolysed, did not produce amide on heating.

Thus although a mixture of trioctylborane, butyl amine and caproic acid may yield amide in high yield the vigorous conditions necessary are unsuitable for peptide synthesis.

The acyloxydialkoxyboranes, $RCO_2B(OR')_2$ (VI) seemed particularly attractive examples of the general type (IV), as there is the possibility of good utilization of the nucleophile in mild, neutral conditions. Acyloxyalkoxyboranes have been proposed[14] as intermediates in the esterification of carboxylic acids by trialkoxyboranes.[14–16]

The trialkoxyboranes are monomeric and do not readily form complexes with Lewis bases.[17] Hydrolysis is rapid,[18,19] reaction proceeding mainly by B—O

cleavage,[19] and transesterification reactions proceed smoothly subject to steric control and either general acid or base catalysis.[20] Amination reactions are surprisingly slow considering that amines are better nucleophiles than alcohols and that trialkoxyboranes are stronger Lewis acids than triaminoboranes.[21]

Caproic acid and trimethoxyborane interacted weakly at room temperature but no ester was produced until addition of a trace of *p*-toluenesulphonic acid, whereupon ester formation was rapid. Therefore a mixture of caproic acid and n-butyl amine was heated with trimethoxyborane and a catalytic quantity of *p*-toluenesulphonic acid. Due to salt formation the reaction was slow inasmuch as amide (78%) was isolated together with acid (12%). Despite the inevitable production of methanol only a trace amount of methyl caproate could be detected. In view of the commercial availablity of trimethoxyborane, the utilization of all the amine and the mild conditions required, the method is a very promising amide synthesis. However, the heating (65°) required renders it unsuitable for a peptide synthesis.

Eq. (3) shows a neutral reaction that might yield acyloxydialkoxyborane. Dimethoxyboron chloride (VII) is readily available from boron trichloride and trimethoxyborane.[22]

$$(3)\qquad RCO^{(2-)}M^{(+)} + \underset{VII}{ClB(OMe)_2} \rightarrow \underset{VIII}{RCO_2B(OMe)_2} \xrightarrow{\text{amine}} \text{Amide}$$

On addition of VII to a suspension of the dry sodium salt of a carboxylic acid a rapid reaction occurs, and the solution shows a band in the IR spectrum at 1710 cm^{-1} that could correspond to VIII. Addition of methanol at room temperature gave no ester. Addition of amine in the cold rapidly gave amide (44%), but despite variation in the acid used as well as the alkoxyborane the yield of amide was always below 50%. The reasons for this are examined in the next paper. Heating increased the yield to CA. 70%.

The method was tested for efficiency in peptide synthesis by the production of benzoyl-L-leucylglycine ethyl ester as suggested by Young.[23] The sodium salt of benzoyl-L-leucine was reacted with VII at room temperature and glycine ethyl ester added (Eq. 4). There was a slight warming and addition of water gave benzoyl-L-leucylglycine ethyl ester (31%) with an optical purity of at least 90%.

$$(4)\qquad PhCOHN\underset{\underset{CH_3}{|}}{C}HCO^{(2-)}Na^{(+)} + ClB(OMe)_2 \rightarrow [PhCONH\cdot\underset{\underset{CH_3}{|}}{CH}\cdot CO_2B(OMe)_2] + NaCl$$

$$\xrightarrow{\text{glysine ethylester}} Ph\,CO\,NH\,\overset{CH_3}{\overset{|}{C}}H\,CO\cdot NH\,CH_2CO_2Et$$

Whilst the high degree of retention was encouraging the low conversion achieved does not, at the moment, make this a viable peptide synthesis. Warming the reaction mixture led to complete racemization whilst the use of more polar solvents also encouraged racemization. The normally heterogeneous nature of the reaction appears to play no part in the low conversions, as in one reaction carried out at higher than usual concentration in benzene, the sodium chloride did not separate out although

reaction had proceeded as indicated by the IR spectrum. The amine was added to the clear solution but a higher conversion was not achieved.

A further route to compounds VII was by addition of acid to a dialkoxyborane. The desired reagents could be produced from di-isopropoxyborane and di-t-amyloxyborane but again reaction with amine only yielded amide with a low conversion. This method is discussed in detail in the following paper.

EXPERIMENTAL

Some amide preparations using tri-n-butylamine borane (IX). The borane IX was prepared according to the method of Abrey and Lappert[24] and had b.p. 65–67°/0·002 mm, $n_D^{23\cdot5}$ 1·4449 (lit. n_D^{20} 1·4460).

N-*Butylphenylacetamide*

Phenylacetic acid (0·51 g) in benzene (6 ml) was added to IX (1·4 g, 1·5 mole equiv) and the mixture heated under reflux for 4 hr. The mixture was diluted with ether (8 ml) and extracted with 2NHCl (2 × 25 ml), saturated $KHCO_3$ aq (2 × 20 ml) and water (2 × 20 ml). The aqueous acid extract was brought to pH 8·0, saturated with NaCl and re-extracted with ether. The organic layers were combined, dried ($MgSO_4$) and the solvent removed to give the amide, m.p. 54–55° (0·65 g, 90%) identical in IR spectrum and m.p. with a pure authentic sample.

N-*Butylpivalamide*

Pivalic acid (0·50 g) in benzene was added to IX (1·70 g, 1·5 mole equiv) and the reaction mixture heated under reflux for 21·5 hr. Work-up as before followed by distillation gave n-butylpivalamide (0·696 g, 90%), b.p. 58–59°/0·2 mm, n_D^{21} 1·4442, identical in all respects with an authentic sample.

N-*Butylcaproamide*

Caproic acid (0·415 g) was heated under reflux with IX (1·31 g, 1·5 mole equiv) in benzene (5 ml) for 3½ hr. Work-up for neutral product gave N-butylcaproamide as a low melting solid, m.p. 17·5–18·5°, b.p. 78–79°/0·005 mm, $n_D^{21\cdot5}$ 1·4466 (0·654 g, 98%). The crude product had the same physical characteristics as a pure authentic sample.

N,N-*Butylsuccindiamide*

Succinic acid (0·262 g) in warm THF was added to IX (2·56 g, 5 mole equiv). A solid separated out which was isolated after about 5 min reflux and seemed to be a mixture of salt and amide; (ν_{max} [Nujol], 3300, 1640, 1540 cm^{-1}). Refluxing for a further 5 min produced a clear soln, but after 30 min more a second solid separated. The THF was removed and the residue taken in $CHCl_3$. The neutral product was isolated as usual to yield the diamide m.p. 187°, M^+ 228·1838 ($C_{12}H_{24}N_2O_2$ requires 228·1839, 0·444 g., 83%).

N-*Butylcaproamide formation using trioctylborane*

Oct-1-ene and n-butylamine were dried over CaH_2. Caproic acid was azeotroped dry with benzene and $BF_3 \cdot Et_2O$ was distilled immediately before use.

(a) Diborane (20% excess) in THF was added to oct-1-ene (1·43 g, 3 mole equiv) in THF (10 ml). Caproic acid (0·49 g, 1 mole equiv) was added to the mixture at −20° followed, after 20 min by butylamine (0·31 g, 1 mole equiv). The reaction mixture was heated under reflux for 6 hr without significant change, the IR spectrum showing bands at 1660 and 1740 cm^{-1} both before and after heating. More butylamine (0·31 g, 1 mole equiv) was added and the soln heated under reflux for 67 hr followed by refluxing in *p*-xylene for 21 hr. The neutral fraction was isolated by standard methods and chromatographed on neutral alumina to yield the amide m.p. 17–19° (eluant, benzene (3), Pentane (2)) (0·658 g, 90%) identical with an authentic sample.

(b) Diborane was passed into a soln of oct-1-ene (1·42 g, 3 mole equiv) in ether (12 ml), until no olefin remained. The ether was removed under press to remove any diborane which remained. Caproic acid (0·490 g, 1 mole equiv) in ether (2 ml), was added to the reaction mixture, (some gas evolved and a small band at 1610 cm^{-1} produced). After 12 hr at room temp the caproic acid band (1740 cm^{-1}) had disappeared, to be replaced by a band at 1610 cm^{-1} (acyloxy–boron compound). Addition of butylamine caused the 1610 cm^{-1} band to be replaced by a band at 1610 cm^{-1}. *p*-Toluenesulphonic acid (5 mg) was added and the reaction left for 11 hr at room temp without any production of amide. After 6 hr at 68° no amide was produced.

Preparation of N-*butylcaproamide using trimethoxyborane*

Trimethoxyborane (3 ml, 7 mole equiv) was added to a mixture of caproic acid (0·516 g, 1 mole equiv) and n-butylamine (0·32 g, 1 mole equiv). *p*-Toluenesulphonic acid (ca. 5 mg) was added and the mixture heated under reflux for 25 hr. The mixture was worked up as usual for neutral product which was chromatographed on neutral alumina. The amide (0·588 g, 78%) was isolated (eluant 4 : 1; benzene : pentane) and a little impure ester (32 mg) (eluant, pentane). From the alkaline extract caproic acid (0·064 g, 12%) was recovered.

N-*Butylcaproamide formation employing chlorodiethoxyborane*

N-butylamine (0·77 g, 2 mole equiv) in pentane (10 ml) was added to chlorodiethoxyborane[25] (b.p. 45·5–46·5°/60 mm) (0·76 g, 1·05 mole equiv) with stirring at −60°. The reaction mixture was allowed to reach room temp, caproic acid (0·615 g, 1 mole equiv) was added and the reaction left for 21 hr. Work-up as usual gave the amide (0·369 g, 41%) and caproic acid (0·109 g, 17%).

N-*Cyclohexylbutyramide*

(a) Chlorodimethoxyborane (2·2 g) was added to a stirred suspension of sodium butyrate (azeotropically dried, 2·14 g) in benzene. After 1 hr the white lumps of carboxylate salt had disappeared and the soln was translucent with suspended NaCl. Cyclohexylamine (1·02 g) was added and the amide formation followed by IR spectroscopy. *p*-Toluenesulphonic acid (3 mg) was added after 2 hr. After leaving at 24° for 48 hr the mixture was worked up for neutral product, to produce the amide (1·46 g, 44%) identical in all respects with a sample made from the acid chloride and amine.

(b) Chlorodimethoxyborane (3·06 g) was added to a warm suspension of dry sodium butyrate (3·12 g) in benzene (40 ml) and the mixture held at 60° for 1 hr. Cyclohexylamine (4·5 g, 1·5 mole equiv) was added and the mixture stirred at 65° for 12 hr. Work-up as before gave the amide (3·24 g, 69%).

*Benzoyl-*L-*leucine sodium salt*

The acid was dissolved in aqueous MeOH and treated with 95% theoretical quantity of dil NaOH aq. The resulting soln was extracted with ether to remove excess acid and the water/MeOH removed at room temp *in vacuo*. The solid Na salt was ground to a fine powder and dried, with regrinding over P_2O_5 in a vacuum desiccator.

*Benzoyl-*L-*leucylglycine ethyl ester*

(a) Chlorodimethoxyborane (0·77 g, 1·1 mole equiv) was added to a gelatinous suspension of dry sodium benzoyl-L-leucinate (1·67 g, 1 mole equiv) in benzene. The gel quickly dispersed and the soln became almost clear, with just a slight opacity. After 18 hr at room temp a 1720 cm^{-1} band (acyloxyborane?) which had appeared did not increase further. (Exposure to air did not affect the band at 1720 cm^{-1}). Freshly distilled glycine ethyl ester (0·82 g) was added and after 15 hr at 24° the band at 1720 cm^{-1} had disappeared.

Ethyl acetate (150 ml) was added and the resulting soln washed (12 ml 2NHCl × 2, $NaHCO_3$aq, H_2O), dried (Na_2SO_4) and the solvent removed *in vacuo* to yield a gum which crystallized with hexane (0·643 g). Recrystallization from EtOH–hexane gave benzoyl-L-leucylglycine ethyl ester m.p. 150–153°, $[\alpha]_D^{23}$ −33·4° (c, 1·38). (Lit. $[\alpha]_D^{20}$ −34·0°, c, 3·1; m.p. 153–155°). The yield was 31%.

(b) Chlorodimethoxyborane (1·09 g, mole equiv) was heated for 20 hr, with the dried sodium benzoyl-L-leucinate (2·44 g, 1 mole equiv) in benzene at 55°. After addition of glycine ethyl ester the reaction was left at 55° for 20 hr and then worked up as previously to give crystalline benzoyl-DL-leucylglycine ethyl ester, m.p. 139°, $]\alpha]_D^{23}$ 0·00°. The IR spectrum was almost identical with the previous product. (Lit.[23] m.p. 146°).

(c) The chlorodimethoxyborane (0·49 g) was added to a suspension of sodium benzoyl-L-leucinate (1·16 g) in acetonitrile (20 ml). There was the usual disappearance of the band at 1580 cm^{-1} and the appearance of a new band at 1740 cm^{-1}. Glycine ester (0·5 ml) was added and the mixture left at room temp for 46 hr (no change from 18 hr).

Work-up as before gave a colourless gum (1·25 g) which, however, contained a little acid. This was removed to yield a yellow gum (310 mg) which crystallized from light petroleum, then EtOAc–light petroleum to give the D,L-peptide, m.p. 135–138°, $[\alpha]_D$ 0·00°.

N-Butylcaproamide formation using di-isopropoxyborane

Diborane was passed into a soln of acetone (1·09 g, 2 mole equiv) in pentane at −78° until no ketone remained. Any residual diborane was swept out of the soln in a stream of N_2, the mixture brought to 0° and caproic acid (1·09 g, 1 mole equiv) was added over 15 min with stirring. After 45 min at 0° the reaction mixture was brought to 24° and n-butylamine (0·69 g, 1 mole equiv) was added. Amide was present after 20 min and its concentration did not increase after a further 12 hr. Work-up for neutral product gave the amide (0·708 g, 44%) and caproic acid (0·556 g, 51%) was recovered from the alkaline washings.

N-Butylcaproamide formation using di-t-amyloxyborane

Diborane (4 mmole) in THF (10 ml) was cooled to 0° and t-amyl alcohol (1·41 g, 16·1 mmole) was added. Gas evolution became slow after ca. 13 mmole H_2 had been collected. The mixture was brought to 24° and caproic acid (0·719 g, 6·2 mmole) was added. There was a slow evolution of gas and 5·5 mmole was collected over 16 hr. n-Butylamine (0·433 g, 5·5 mmole) was added, when amide formation was rapid (virtually complete at 25 min). Standard work-up gave the amide (0·322 g, 29·5%) and caproic acid (0·448 g, 66·5%).

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