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Use of mesityllithium in the α-alkylation reaction of B-alkyl-9-borabicyclo[3.3.1]nonanes

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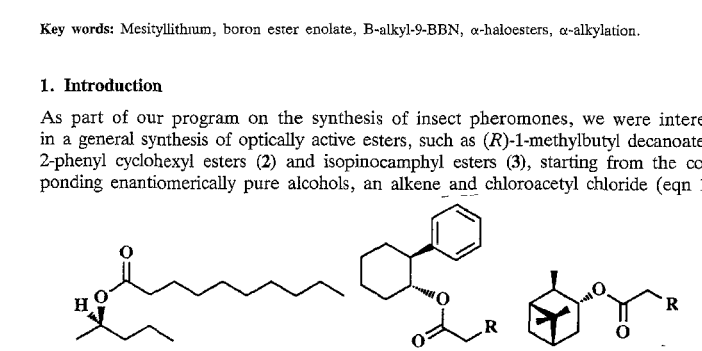
Abstract

Reaction of α-chloro and α-bromo esters with B-alkyl-9-borabicyclo[3.3.1]nonanes, B-alkyl-9-BBN, in the presence of the bulky carbon base, mesityllithium, was studied. The trialkylboranes containing primary B-alkyl groups reacted readily to give the corresponding esters. However, the reaction of trialkylboranes containing secondary B-alkyl groups was sluggish. The product esters were isolated by a non-oxidative workup. Use of mesityllithium in this α-alkylation reaction permitted trapping of the intermediate boron ester enolate using benzaldehyde. However, the aldol product thus obtained was a mixture of *syn* and *anti* isomers.

Key words: Mesityllithium, boron ester enolate, B-alkyl-9-BBN, α-haloesters, α-alkylation.

1. Introduction

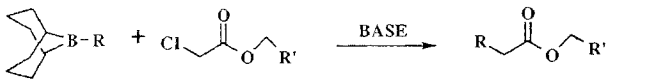
As part of our program on the synthesis of insect pheromones, we were interested in a general synthesis of optically active esters, such as (*R*)-1-methylbutyl decanoate (**1**), 2-phenyl cyclohexyl esters (**2**) and isopinocamphyl esters (**3**), starting from the corresponding enantiomerically pure alcohols, an alkene and chloroacetyl chloride (eqn 1).



(1)

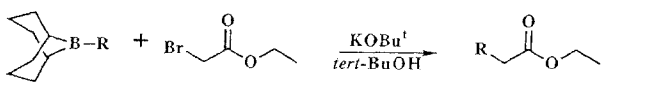
* For correspondence.

Since it is known that B-alkyl-9-borabicyclo[3.3.1]nonanes, B-alkyl-9-BBN, react with ethyl haloacetate under the influence of a base to give the corresponding homologated esters[1-3], we anticipated that B-alkyl-9-BBN would react with an optically active chloroacetate to give the corresponding optically active esters. Optically active esters can be obtained from three components: optically active alcohol, alkene and chloroacetyl chloride (eqn 1). Chloroacetyl chloride can be combined with the alcohol to form the corresponding α-haloesters. The alkene can be hydroborated with 9-BBN to give the B-alkyl-9-BBN which can react with the α-haloester in the presence of a base to give the desired homolagated ester (eqn 2).



(2)

The well-established procedure for the above reaction is to react B-alkyl-9-BBN with bromoethyl acetate in the presence of potassium *t*-butoxide in *t*-butanol[1,2]. Later on, this procedure was modified with the use of potassium 2,6-di-*tert*-butyl phenoxide as the base in tetrahydrofuran (THF). However in the later reaction, the ester has to be separated from the byproduct, 2.6-di-*tert*-butyl phenol, by a tedious column chromatographic procedure (eqns 3 and 4)[2].



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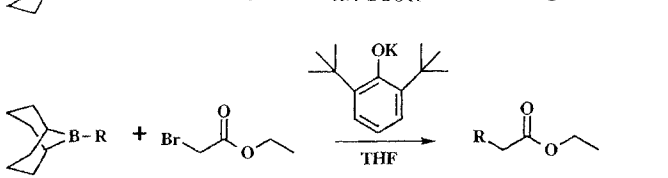


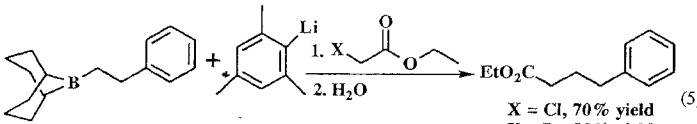
(4)

Recently, this procedure has been extended to include optically active B-alkyl-9-BBN derivatives[3]. It has been suggested that these α-alkylation reactions proceed through the intermediate formation of the corresponding boron ester enolates[3,4]. However, no evidence for the formation of this intermediate has been presented. Herein, we report the use of mesityllithium, a bulky carbon base, for this α-alkylation reaction which allowed us to trap the intermediate boron ester enolate.

2. Results and discussion

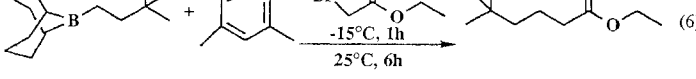
Boron ester enolates are generally unstable in the presence of alcohols and phenols, produced during the deprotonation step in the α-alkylation reaction, and undergo a rapid protonolysis to afford the product ester. Consequently, isolation of boron ester

enolate intermediates is difficult. In order to trap the intermediate boron ester enolate, we needed a non-alkoxide base that will be satisfactory in the α-alkylation reaction. Although a number of promising bases are available, we selected mesityllithium[5] for our study since it is expected to produce the hydrocarbon mesitylene after the deprotonation step. Moreover, we speculated that the presence of the two *ortho*-methyl groups might prevent any strong complexation of the base with the B-alkyl-9-BBNs. Consequently, we examined the α-alkylation of ethyl chloroacetate using representative B-alkyl-9-BBNs in the presence of mesityllithium. Our experimental procedure involved addition of mesityllithium to a THF solution of the trialkylborane and ethyl chloroacetate at −15°C, stirring at 25°C for 6 h and quenching the reaction with water. We observed high yields of the corresponding homologated esters with all of the trialkylboranes. The yield of the homologated ester improved when ethyl bromoacetate was used as the substrate instead of the chloroacetate (eqn 5).



(5)

We then extended this reaction to other B-alkyl-9-BBN derivatives of varying steric requirements and found that the α-alkylation of ethyl bromoacetate using trialkylboranes proceeds efficiently in the presence of mesityllithium. Transfer of the primary alkyl group from boron to carbon was relatively facile compared to the transfer of the secondary alkyl group (eqns 6 and 7).



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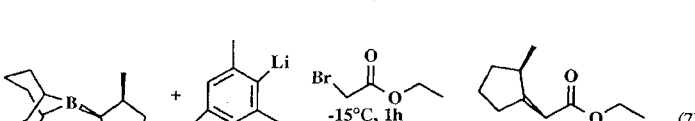


(7)

The yields observed were in the range of 50–82%, indicating some competition between migration of the B-alkyl group and the B-cyclooctyl group (Table I).

As pointed out earlier, it has been suggested that these α-alkylation reactions proceed through the intermediate formation of the corresponding boron–ester enolates[3,4].

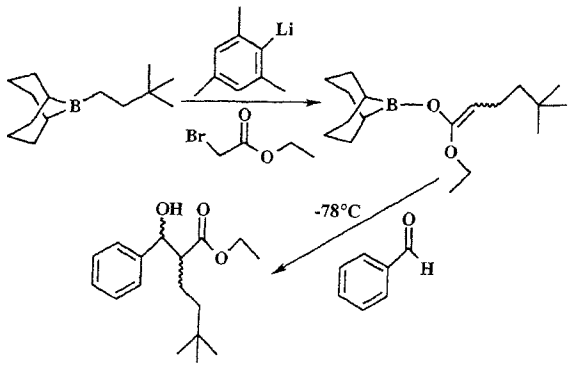
Table I

Alkylation of ethyl bromoacetate with B-R-9-BBNs[a]

B-R-9-BBN, R=	*Product*	*IY,[c] (%)*	*bp, °C(torr)*
1-octyl	ethyl decanoate	80	102–104(7)
3,3-dimethyl-1-butyl	ethyl 5,5-dimethylhexanoate	82	74–76(5)
2-butyl	ethyl 3-methylpentanoate	65	68–70(25)
3-methyl-2-butyl	ethyl 3,4-dimethylpentanoate	60	82–84(20)
trans-2-methylcyclopentyl	ethyl *trans*-2-methylcyclopentyl acetate	55	98–100(20)
2-phenylethyl	ethyl 4-phenylbutanoate	50	90–92(0.4)

[a]Unless otherwise indicated, all reactions were carried out in tetrahydrofuran at −15°C for 1 h and then at 25°C for 6 h using mesityllithium as the base. [b]Organoboranes were prepared by the hydroboration of the corresponding alkenes using 9-BBN. [c]Isolated yield.

After establishing the use of mesityllithium in the α-alkylation reaction, we attempted to trap the intermediate boron ester enolate by quenching the reaction mixture with benzaldehyde. The α-alkylation reaction was carried out using B-3,3-dimethyl-1-butyl-9-borabicyclo[3.3.1]nonane, ethyl bromoacetate and mesityllithium as described before. The reaction mixture was then cooled to −78°C and treated with an equimolar quantity of benzaldehyde. The reaction mixture was allowed to come to 25°C slowly over a period of 12 h. The solvent THF was evaporated at reduced pressure (20 torr, 25°C) and the residue was taken up in *n*-pentane. The organic phase was washed successively with water and sodium hydroxide to remove lithium bromide and 9-BBN residue respectively. The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure (10 torr, 25°C) to obtain the aldol product, ethyl 2-(hydroxyphenylmethyl)-5,5-dimethylhexanoate, in 95% yield. However, the ^{1}H NMR spectral analyses showed the product to be a mixture of *syn* and *anti* products (eqn 8).



(8)

95% crude yield, *syn* : *anti* = 50:50

3. Conclusion

This study demonstrates that the α-alkylation of chloroacetates and bromoacetates using B-alkyl-9-BBNs can be achieved with the carbon base mesityllithium. Use of mesityllithium in this reaction leads to stable boron ester enolate intermediates which, on quenching with water, afford the desired homologated esters. The intermediate boron ester enolates can be trapped with benzaldehyde. However, the aldol product was obtained as a 1:1 mixture of *syn* and *anti* isomers.

4. Experimental

All operations were carried out under a nitrogen atmosphere. All glassware, syringes and needles were oven dried and cooled under a nitrogen atmosphere. THF was freshly distilled from sodium and benzophenone ketyl. Anhydrous ether (Et_2O) was purchased from Fisher and was used directly. Ethyl bromoacetate, ethyl chloroacetate, 9-BBN, mesityl bromide and all the alkenes were purchased from Aldrich Chemical Company, stored under nitrogen.

^{11}B NMR spectra were obtained with a Bruker ACF 250 MHz spectrometer and the chemical shifts are in δ relative to $Et_2O.BF_3$-with chemical shifts downfield from $Et_2O.BF_3$-assigned positive. ^1H NMR and ^{13}C NMR were recorded on a Brucker ACF 250 MHz spectrometer. Chemical shifts are in δ relative to Me_4Si.

Microanalyses were carried out by the Purdue Microanalytical Laboratory. Capillary gas chromatography was carried out with a Hewlett–Packard 5890 chromatograph fitted with a 30-m methylsilicone column. Optical rotations were measured on a JASCO DIP-370 digital polarimeter and are reported as observed rotations. Mass spectra (EI) were obtained on Finnigan 4000 mass spectrometer with Super Incos data system.

4.1. Alkylation of ethyl with B-alkyl-borabicyclo[3.3.1]nonanes in the presence of mesityllithium

The following procedure for the synthesis of ethyl decanoate is representative. A 1.0 M THF solution of B-octyl-9-BBN (20 ml, 20 mmol) was cooled to −15°C (ice-salt bath), and freshly prepared 0.5 M solution of mesityllithium (40 ml, 20 mmol) was then added to it. The ^{11}B NMR spectrum of an aliquot showed a singlet at δ+79 indicating the absence of any complex formation with the base. Ethyl bromoacetate (3.34 g, 20 mmol) was then added slowly with constant stirring. The reaction mixture was stirred at −15°C for 1 h and then at 25°C for 6 h. The ^{11}B NMR of an aliquot showed a singlet at δ+56 and the absence of the peak at δ+79 due to the starting trialkylborane. Solvent (THF) was evaporated under reduced pressure (25°C, 20 torr). The residue was taken up with *n*-pentane (100 ml) and washed successively with 3.0 M NaOH (3×10 ml) and water (2×10 ml), and the organic phase dried over anhydrous $MgSO_4$. The solvent was evaporated (25°C, 12 torr) and the residue was distilled to obtain a mixture of ethyl decanoate and mesitylene. Pure ethyl decanoate was isolated from this mixture by a plug-filtration over SiO_2-gel. Using *n*-pentane as the eluant, mesitylene was separated from the ester. An ether wash of the column gave

ethyl decanoate which was purified by distillation: 3.2 g, 80% yield, bp 102–104°C (7 torr), ^{1}H NMR ($CDCl_3$ 0.85(t, J=7 Hz, 3H), 1.19–1.85(m, 17H), 2.24(t, J=6.5 Hz, 2H), 4.10(q, J=7 Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.1, 14.2, 22.6, 25.0, 29.2, 31.8, 34.4, 60.1, 173.9. MS (m/z) 200 (M+1). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95, H, 12.08. Found: C, 71.90; H, 12.17.

Ethyl 3-methylpentanoate: ^{1}H NMR ($CDCl_3$), 0.92(m, 6H), 1.09–1.45(m, 2H), 1.26(t, J=7 Hz, 3H), 1.70–1.90(m, 1H) 2.03(dd, J=10, 14 Hz, 1H), 2.32(dd, J=6,14 Hz, 1H), 4.12(q, J=7 Hz, 2H). ^{13}C NMR ($CDCl_3$) 11.0, 14.1, 19.0, 29.2, 31.8, 41.3, 59.8, 172.9 Anal. Calcd for $C_8H_{16}O_2$: C, 66.63, H, 11.19. Found: C, 66.82; H, 11.32.

Ethyl 3,4-dimethylpentanoate: ^{1}H NMR ($CDCl_3$) 0.86(m, 9H), 1.26(t, J=7 Hz, 3H), 1.78(m, 1H), 1.9(m, 1H), 2.08(dd, J=10, 16 Hz, 1H), 2.36 (dd, J=6, 16 Hz, 1H), 4.13 (q, J=7 Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.1, 15.7, 18.2, 19.7, 21.1, 35.9, 39.2, 59.9, 173.4. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.40; H, 11.57.

Ethyl trans-2-methylcyclopentylacetate: ^{1}H NMR ($CDCl_3$) 0.98(d, J=7 Hz, 3H), 1.26(t, J=7 Hz, 3H), 1.28–2.04(m, 8H), 2.12(dd, J=9, 15 Hz, 1H), 2.46(dd, J=5, 15 Hz, 1H), 4.13(q, J=7 Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.2, 18.9, 23.3, 32.4, 34.5, 39.4, 40.5, 44.1, 59.9, 173.3. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.56; H, 10.8.

Ethyl 5,5-dimethylhexanoate: ^{1}H NMR ($CDCl_3$) 0.73(s, 9H), 1.13(t, J=7 Hz, 3H), 1.27–1.80(m, 4H), 2.29(t, J=5 Hz, 2H), 4.03(dd, J=3, 7 Hz, 2H). ^{13}C NMR ($CDCl_3$) 14.1, 25.5, 27.1, 29.2, 29.7, 32.1, 60.0, 173.6. MS (m/z): 172 (M+1). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.53, H, 11.94.

Ethyl 4-phenylbutanoate: ^{1}H NMR ($CDCl_3$) 1.26(t, J=7 Hz, 3H), 1.48–2.05(m, 2H), 2.24(t, J=7 Hz, 2H), 2.68(t, J=7 Hz, 2H), 4.16(q, J=7 Hz, 2H), 7.22(s, 5H). ^{13}C NMR ($CDCl_3$) 14.3, 22.1, 26.6, 32.3, 60.4, 126.0, 128.4, 141.3, 173.9. MS (m/z): 192 (M+1). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.12; H, 8.31.

Ethyl 2-(hydroxyphenylmethyl)-5,5-dimethylhexanoate: To a nitrogen-cooled round bottom flask, charged with a magnetic stirring bar, a freshly prepared 1.0M B-3,3-dimethyl-1-butyl-9-borabicyclo[3.3.1]nonane solution (15 mmoles) and ethyl bromoacetate (15 mmoles) were added. The mixture was cooled to −15°C and stirred for about 15 minutes. Mesityllithium (15 mmoles) was then added dropwise. After 15 min from the addition of the base, the ice bath was taken away and the reaction mixture was allowed to react at 25°C for 3 h. This solution was cooled to −78°C and freshly distilled benzaldehyde (15 mmoles) was added to it. The reaction mixture was allowed to reach 25°C and stirred overnight. The THF was evaporated at reduced pressure (20 torr) and the residue was taken up in pentane (100 ml) and poured in a sep. funnel. The organic phase was washed with water (3 × 20 ml) to get rid of the LiBr and then with 3.0 M NaOH (3 × 10 ml) to get rid of the 9-BBN residue. The organic phase was dried over anhydrous magnesium sulfate. The solution was filtered and the solvent evaporated at reduced pressure (10 torr, 25°C) to afford crude ethyl 2-(hydroxyphenylmethyl)-5,5-dimethylhexanoate as a viscous liquid in 95% yield. ^{1}H NMR showed this to be a 1:1 mixture of *syn* and *anti* isomers.

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