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DIRECTIVE EFFECTS IN THE HYDROBORATION OF ISOMERIC METHOXY-2-HEXYNES

GEORGE W. KABALKA* and SUZANNE SLAYDEN

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916 (U S.A.)

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Summary

A series of isomeric methoxy-2-alkynes were hydroborated to determine the effect of the methoxy group on the direction of the hydroboration. The effect of the methoxy group is to direct the boron atom to the side of the triple bond nearest to it. The magnitude of the directive effect increases as the methoxy group approaches the site of unsaturation. However, steric interactions become significant when the substituent is adjacent to the triple bond.

Introduction

The hydroboration reaction has become increasingly important in recent years [1]. The importance of hydroboration as a synthetic technique is enhanced by the fact that a wide variety of functionalities are unaffected by the hydroborating reagents [2]. Functional substituents may, however, affect the regiospecificity of the hydroboration reaction and considerable attention has been directed toward studies of the hydroboration of functionally substituted olefins [3-5].

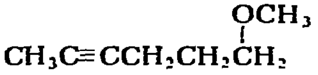
In contrast to the alkene studies, little is known concerning substituent effects in the hydroboration of substituted alkynes [6-9]. It would appear that inductive effects could operate in the hydroboration of alkynes as they do in the case of alkenes.

We wish to report the results of a systematic study of the substituent effects on the regiospecificity of the monohydroboration of alkynes.

Results

A series of isomeric methoxyhexynes was synthesized and hydroborated. The methoxy group was chosen because it exhibits a strong inductive effect and because alkoxyorganoboranes are not prone to elimination reactions [10]. Dicyclohexylborane was used as the hydroborating agent. Dialkylboranes react cleanly with alkynes to yield vinyldialkylboranes which may be readily oxidized to the corresponding ketones [11]. When borane ($BH_3 \cdot THF$) was employed as the hydroborating reagent, material balances were poor due to dihydroboration [12], and consequently the observed ketone isomer distribution might not reflect the actual distribution of boron in the intermediates*.

The compounds hydroborated were the 6- (I), 5- (II), 4- (III), and 1-methoxy-2-hexyne (IV).

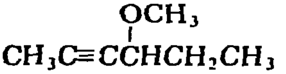


$CH_3C{\equiv}CCH_2CH_2\overset{OCH_3}{\overset{|}{C}}H_2$

(I)

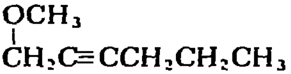
$CH_3C{\equiv}CCH_2\overset{OCH_3}{\overset{|}{C}}HCH_3$

(II)



$CH_3C{\equiv}\overset{OCH_3}{\overset{|}{C}}CHCH_2CH_3$

(III)



$\overset{OCH_3}{\overset{|}{C}}H_2C{\equiv}CCH_2CH_2CH_3$

(IV)

The resultant organoboranes were oxidized to the corresponding ketones and the products analyzed by NMR and GLPC. The overall sequence is illustrated for 6-methoxy-2-hexyne (Scheme 1). The results are summarized in Table 1.

SCHEME 1

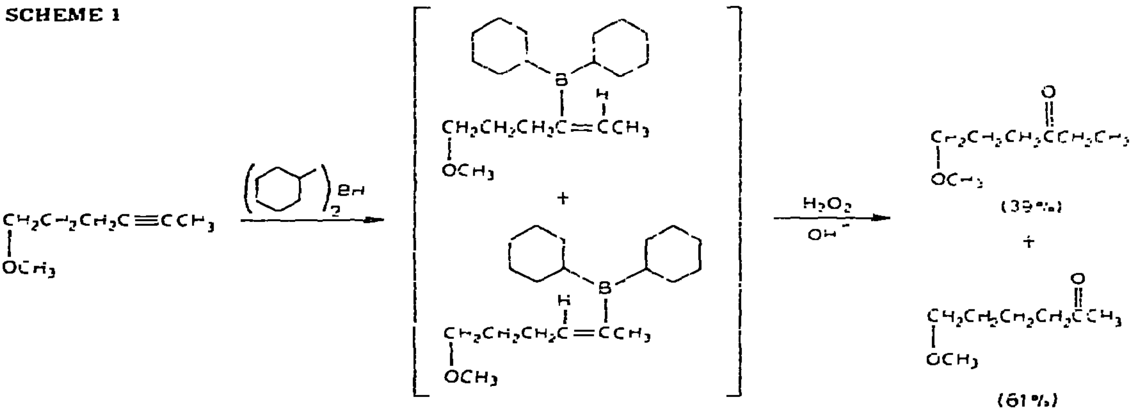


TABLE 1

THE HYDROBORATION OF A SERIES OF METHOXY-2-HEXYNES WITH DICYCLOHEXYLBORANE

Alkyne	Yield of ketones[a] (%)	2-Ketone[a,b] (%)	3-Ketone[a,b] (%)
2-Hexyne	98	67	33
6-Methoxy-2-hexyne	96	61	39
5-Methoxy-2-hexyne	98	39	61
4-Methoxy-2-hexyne	99	72	28
1-Methoxy-2-hexyne	85	80	20

[a] Yields and percentages were determined by NMR and GLPC analyses using appropriate internal standards.
[b] Products were isolated by preparative GLPC. They were characterized as the corresponding 2,4-dinitrophenylhydrazones. All exhibited satisfactory spectral and elemental analyses.

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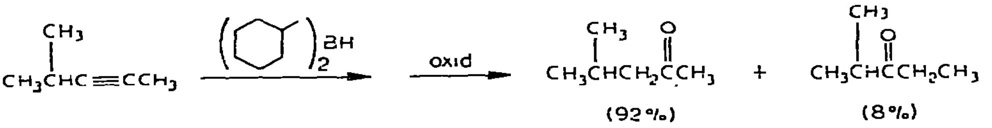
* It is interesting to note that we observed ketone isomer distributions for $BH_3 \cdot THF$ hydroborations parallel to those for dicyclohexylborane, except in hydroboration of 4-methoxy-2-hexyne where steric interactions for dicyclohexylborane would be expected to be larger than for borane itself.

Discussion

The results demonstrated that with one exception, the directive influence of a methoxy group in the hydroboration of 2-hexyne appears to operate in the same direction as that observed in the hydroboration of functionally substituted alkenes. As in the alkene studies, the inductive effect of the methoxy group increases as it is brought nearer to the unsaturated center. This is evidenced by the larger percentage of the 3-ketone isomer obtained in the hydroboration—oxidation of 5-methoxy-2-hexyne than in the hydroboration of 6-methoxy-2-hexyne.

The hydroboration—oxidation of 4-methoxy-2-hexyne produces more of the 2-ketone isomer than might be expected on the basis of an inductive effect. However, the results may be explained by assuming that α-substituted alkynes sterically hinder the approach of the bulky hydroborating agent. For example, it has been reported that the hydroboration of 4-methyl-2-pentyne with dicyclohexylborane yields 92% of the 2-ketone isomer after oxidation (eqn. 1), as compared to 67% for 2-hexyne itself [11]. The approach of dicyclohexylborane to 4-methoxy-2-hexyne would be expected to experience a steric interaction similar to that experienced in an approach to 4-methyl-2-pentyne. Comparison of the distribution ratio of the product ketones in the 4-methoxy-2-hexyne reaction to those found for 4-methyl-2-pentyne would then be a more realistic appraisal of the inductive effect of the methoxy group. Thus, replacement of a methyl substituent by a methoxy substituent in 4-substituted-2-hexynes increases the amount of 3-ketone significantly (39/61 versus 8/92). Viewed in this light, the methoxy group does indeed exhibit a strong inductive effect.



(1)

In order to test the hypothesis that steric interactions in the hydroboration of 4-methoxy-2-hexyne interfere with the inductive effect of the methoxy group, 1-methoxy-2-hexyne was hydroborated and oxidized. Little if any steric interaction would be expected in this case, since a methoxymethylene group is sterically similar to a n-propyl group. The results confirm our expectation, in that the boron atom is directed towards the methoxy substituent.

In summary, the directive effect of the methoxy group (and presumably other *—I* groups) in the hydroboration of alkynes essentially parallels that found in the hydroboration of functionally substituted alkenes*.

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* As a referee noted, the directive effect observed in the hydroboration—oxidation of the β-methoxy-2-hexyne appears to be more intense than that found in the hydroboration of β-alkoxyalkenes. To be specific, the hydroboration—oxidation of 2-hexyne yields 33% of the 3-ketone whereas the hydroboration—oxidation of 5-methoxy-2-hexyne yields 61% of the 3-ketone (an increase of 28%). In contrast, the hydroboration—oxidation of 4-methoxycyclohexene yields 56% of the β-hydroxy derivative as compared to the 50/50 distribution observed in cyclohexene itself (an increase of only 6%) [5]. A possible explanation would involve an internal complexation between the dicyclohexylborane and the methoxy group prior to the hydroboration reaction thus orienting the boron to the 3-position. We are exploring this possibility.

Experimental

Reagents. 1-Pentyn-5-ol, 2-hexyn-1-ol, and 2-hexyn-5-ol were purchased from Farchan Chem. Co. and used as received.

Analyses. NMR analyses were performed on a Varian Associates Model A-60 spectrometer. Analytical GLPC analyses were performed on Varian Aerograph 1700 and 90-P instruments using a 10′ column, 6% Carbowax on Chromosorb W. Preparative GLPC was performed on Varian Aerograph 711 using a 20′ column, 30% FFAP on Chromosorb W. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee and Microanalytical Laboratories, Oxford, England.

Alkynes

6-Methoxy-2-hexyne (I). The compound was prepared by the reaction of two equivalents of sodamide with 1-pentyn-5-ol, followed by addition of two equivalents of methyl iodide [13]. Yield, 31 g (0.28 mol, 55%); b.p. 146°C/739 Torr. NMR (neat): δ 3.17 (2H, t, J = 6 Hz, $-C\underline{H}_2-OCH_3$), 3.07 (3H, s, CH_3O-). 1.9 (2H, m, $-C{\equiv}C-CH_2-$), 1.52 (3H, t, J = 2.5 Hz, $CH_3C{\equiv}C-$), 1.45 (2H, m, $-CH_2-C\underline{H}_2-CH_2-$). Anal. Found: C, 74.76; H, 10.69. $C_7H_{12}O$ calcd.: C, 74.94; H, 10.80%.

5-Methoxy-2-hexyne (II). The compound was prepared from 2-hexyn-5-ol 49 g (0.5 mol) and methylated by the method of Brandsma [14]. Yield, 44 g (0.39 mol, 78%); b.p. 135-136°C/740 Torr. NMR (CCl_4): δ 3.11 (1H, m, HC), 3.10 (3H, s, CH_3O-), 2.05 (2H, m, $-C{\equiv}C-CH_2-$), 1.57 (3H, t, J = 2 Hz, $CH_3-C{\equiv}C-$), 1.00 (3H, d, J = 6 Hz, $C\underline{H}_3-CH-$). Anal. Found: C, 74.90; H, 10.71. $C_7H_{12}O$ calcd.: C, 74.94; H, 10.80%.

4-Methoxy-2-hexyne (III). 4-Hydroxy-2-hexyne was prepared according to published procedure [15]. The methyl ether derivative was then prepared by the method of Brandsma [14]. B.p. 124-125°C/740 Torr. NMR (CCl_4): δ 3.67 (1H, m, $-C{\equiv}C-CH$), 3.24 (3H, s, CH_3O-), 1.65 (3H, d, J = 2.5 Hz, $CH_3C{\equiv}C-$), 1.47 (2H, m, $CH_3-C\underline{H}_2-$), 0.87 (3H, t, J = 7 Hz, $C\underline{H}_3CH_2-$). Anal. Found: C, 74.86; H, 10.88. $C_7H_{12}O$ calcd.: C, 74.94; H, 10.80%.

1-Methoxy-2-hexyne (IV). The compound was prepared from 2-hexyn-1-ol by the method of Brandsma [14]. Yield, 48 g (0.43 mol, 86%); b.p. 139.5-140.5°C/740 Torr. NMR (CCl_4): δ 3.82 (2H, t, J = 2 Hz, $CH_3O-C\underline{H}_2-$), 3.08 (3H, s, CH_3O-), 1.95 (2H, m, $-C{\equiv}C-C\underline{H}_2CH_2-$), 1.3 (2H, m, $CH_3C\underline{H}_2-$), 0.77 (3H, t, J = 6.5 Hz, $C\underline{H}_3CH_2-$). Anal. Found: C, 74.78; H, 10.82. $C_7H_{12}O$ calcd.: C, 74.94; H, 10.80%.

Monohydroboration of methoxyalkynes

The following procedure for the hydroboration of the alkynes with dicyclohexylborane is representative. To a suspension of dicyclohexylborane (11 mmol) in tetrahydrofuran (THF) was added at −10·0°C the appropriate alkyne (10 mmol). The reaction mixture was stirred at −10·0°C for 1 h and at room temperature for 1 h. The resulting vinylborane was oxidized by adding 3.65 ml of 3 *N* sodium hydroxide and 3.30 ml of 30% hydrogen peroxide to the reaction mixture. The cyclohexanol and ketone products formed were extracted with diethyl ether and dried over anhydrous magnesium sulfate. The distribution of ketones was determined by GLPC (except IV). The yield of ketone was determined by NMR using benzene as an internal reference. The ketones were isolated by preparative GLPC.

Products from the hydroboration of 6-methoxy-2-hexyne (I)

6-Methoxyhexan-2-one. NMR (CCl_4): δ 3.22 (2H, t, J = 5.5 Hz, $CH_3OC\underline{H}_2$—), 3.17 (3H, s, CH_3O—), 2.3 (2H, t, J = 6.5 Hz, —$CH_2C{=}O$), 1.97 (3H, s, $CH_3C{=}O$), 1.42 (4H, m, —CH_2—$C\underline{H}_2C\underline{H}_2$—$CH_2$—); 2,4-DNPH m.p. 68-69°C [lit. [16] 60-70°].

6-Methoxyhexan-3-one. NMR (CCl_4): δ 3.27 (2H, t, J = 5.5 Hz, $CH_3OC\underline{H}_2$—), 3.21 (3H, s, CH_3O—), 2.57-2.10 (4H, m, —$C\underline{H}_2COC\underline{H}_2$—), 1.68 (2H, m, CH_2—$C\underline{H}_2$—CH_2—), 0.95 (3H, t, J = 7.5 Hz, $C\underline{H}_3CH_2$—). The pure 2,4-DNPH derivative of the ketone could not be obtained. An analysis of the isomeric ketone derivative mixture and the composite NMR spectrum are consistent with this product [16]. Anal. Found: C, 50.16; H, 5.77; N, 18.06. $C_{13}H_{18}N_4O_5$ calcd.: C, 50.31; H, 5.86; N, 18.05%.

Products from the hydroboration of 5-methoxy-2-hexyne (II)

5-Methoxyhexan-2-one. NMR (CCl_4): δ 3.22 (1H, m, HC), 3.22 (3H, s, CH_3O—), 2.4 (2H, t, J = 7 Hz, —$CH_2C{=}O$), 2.05 (3H, s, $CH_3C{=}O$), 1.6 (2H, m, CH_2—$C\underline{H}_2$—CH), 1.05 (3H, d, J = 6 Hz, $C\underline{H}_3CH$); 2,4-DNPH m.p. 67-68°C. Anal. Found: C, 49.99; H, 5.77; N, 18.33. $C_{13}H_{18}N_4O_5$ calcd.: C, 50.31; H, 5.86; N, 18.05%.

5-Methoxyhexan-3-one. NMR (CCl_4): δ 3.68 (1H, m, $\underline{H}C$—OCH_3), 3.23 (3H, s, CH_3O—), 2.41 (4H, m, —$C\underline{H}_2COC\underline{H}_2$—), 1.07 (3H, d, J = 6 Hz, $C\underline{H}_3CH$), 0.97 (3H, t, J = 7.5 Hz, $C\underline{H}_3CH_2$—); 2,4-DNPH derivative isolated as the α,β-unsaturated hydrazone [17], m.p. 112-112.5°C [lit. [18] m.p. 121°]. NMR ($CDCl_3$): δ 6.63-6.27 (2H, vinyl), 2.62 (2H, q, J = 7.5 Hz, —CH_2—$C{=}N$), 2.0 (3H, m, $C\underline{H}_3$-$CH{=}CH$—), 1.23 (3H, t, J = 7.5 Hz, $C\underline{H}_3CH_2$—).

Products from the hydroboration of 4-methoxy-2-hexyne (III)

4-Methoxyhexan-2-one. NMR (CCl_4): δ 3.4 (1H, m, HC), 3.13 (3H, s, CH_3O—), 2.34 (2H, m, —$CH_2C{=}O$), 1.97 (3H, s, $CH_3C{=}O$), 1.33 (2H, m, CH_3-$C\underline{H}_2$—), 0.72 (3H, t, J = 6.5 Hz, $C\underline{H}_3CH_2$—). 2,4-DNPH derivative was isolated as the α,β-unsaturated hydrazone [17], m.p. 166-167°C [lit. [19] m.p. 162-163.5°]. NMR ($CDCl_3$): δ 6.48 (2H, vinyl), 2.65-2.05 (2H, m, —CH_2—), 2.22 (3H, s, CH_3-$C{=}N$), 1.15 (3H, t, J = 7.5 Hz, $C\underline{H}_3CH_2$—).

4-Methoxyhexan-3-one. NMR (CCl_4): δ 3.33 (1H, t, J = 6 Hz, CH), 3.25 (3H, s, CH_3O—), 2.38 (2H, q, J = 7 Hz, —$C\underline{H}_2$—CH_3), 1.52 (2H, m, CH_3—$C\underline{H}_2$—CH), 0.9 (6H, m, 2 CH_3—). The pure 2,4-DNPH-α,β-unsaturated hydrazone derivative could not be isolated. The NMR spectrum of the isomeric hydrazone mixture was consistent with this product.

Products from the hydroboration of 1-methoxy-2-hexyne (IV)

1-Methoxyhexan-2-one. NMR (CCl_4) δ 3.8 (2H, s, $CH_3OC\underline{H}_2$—), 3.35 (3H, s, CH_3O—), 2.37 (~2H, m, CH_2CO), 1.33 (~4H, m, $CH_3C\underline{H}_2C\underline{H}_2$—), 0.83 (~3H, $C\underline{H}_3$—CH_2—); 2,4-DNPH m.p. 91-92°C [lit. [20] m.p. 93°]. NMR ($CDCl_3$): δ 4.36 (2H, s, $CH_3OC\underline{H}_2$—), 3.60 (3H, s, CH_3O—), 2.36 (2H, t, J = 7 Hz, —$C\underline{H}_2$-$C{=}N$), 1.53 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$—), 0.95 (3H, t, J = 6 Hz, $C\underline{H}_3$—CH_2—).

1-Methoxyhexan-3-one was observed as an impurity in the 1-methoxyhexan-2-one material. Repeated attempts to isolate this material were fruitless. The isomers were inseparable by GLPC. The NMR spectrum of the 2-ketone indicated a maximum of 20% of the 3-ketone as an impurity. NMR (CCl_4): δ 3.5 (2H, t, J = 6.5 Hz, $CH_3O{-}C\underline{H}_2{-}$), 3.22 (3H, s, $CH_3O{-}$), 2.37 (~4H, $-C\underline{H}_2COC\underline{H}_2-$), 1.33 (~2H, $CH_3C\underline{H}_2-$), 0.83 (~3H, $C\underline{H}_3CH_2-$).

Acknowledgement

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