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HIGHLY REGIOSELECTIVE GENERATION OF "THERMODYNAMIC" ENOLATES AND THEIR DIRECT CHARACTERIZATION BY NMR[1]

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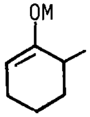
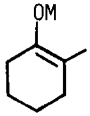
SUMMARY: Addition of 2-methylcyclohexanone to 1.05 equiv of KH suspended in THF, followed by treatment with 1.25 equiv of BEt_3 gives potassium enoxyborate **2a** as a 90-95% regioisomerically pure species, as judged by its ^1H and ^{13}C NMR as well as by GLC analysis of the silylated products, while the use of $KN(SiMe_3)_2$ in place of KH gives **1a** as a 90-95% pure substance. The KH-BEt_3 procedure also gives **4** and **5** as 91 and 85% regiochemically pure species, respectively.

We wish to report a direct spectroscopic characterization of both "kinetic" and "thermodynamic" potassium enoxyborates (**1a** and **2a**) obtained from 2-methylcyclohexanone as 90-95% regioisomerically pure species. The preparation of **1a** involves addition of 2-methylcyclohexanone to 1.05 equiv of $KN(SiMe_3)_2$ in THF[2] for 30 min at -78°C followed by treatment with 1.25 equiv of BEt_3 at -78°C,[3] while the use of KH suspension in THF at room temperature[2] in place of $KN(SiMe_3)_2$ provides **2a**.

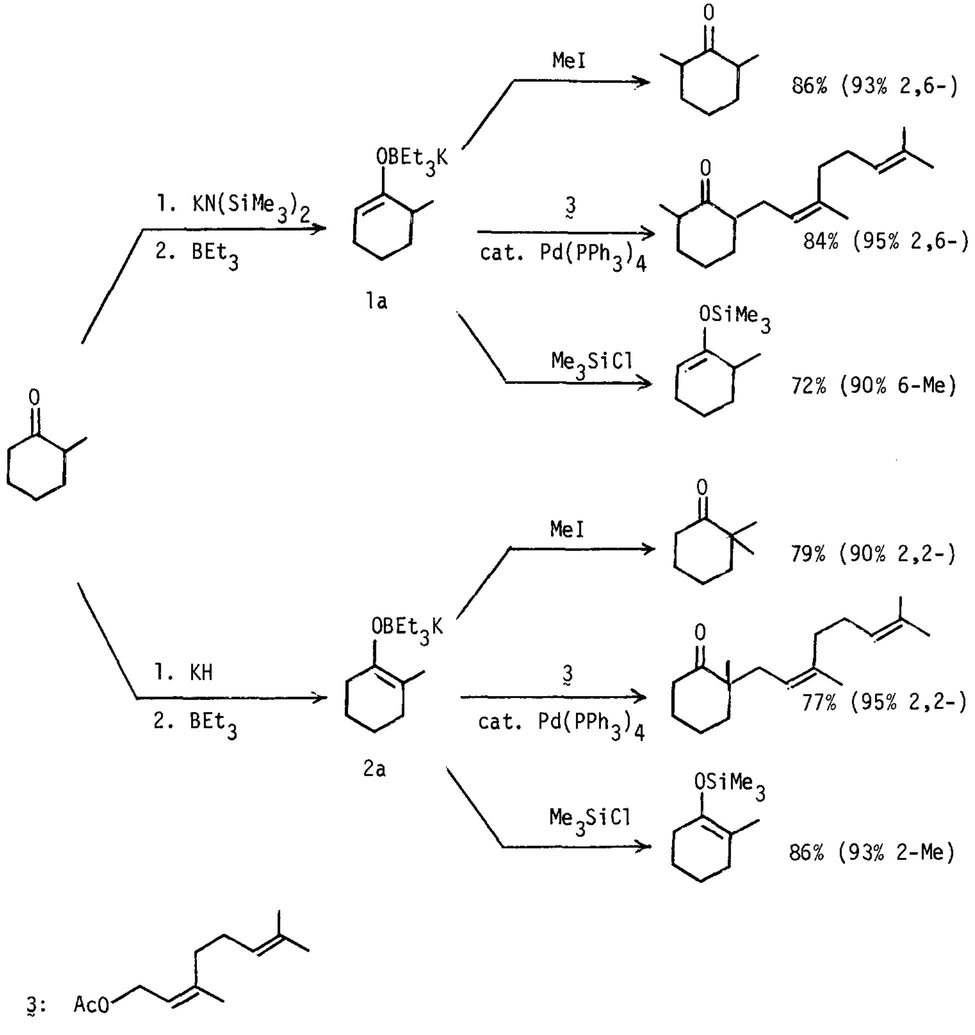


1 (**a**: M = $KBEt_3$, **b**: M = K, **c**: M = Li, **d**: M = $SiMe_3$)



2 (**a**: M = $KBEt_3$, **b**: M = K, **c**: M = Li, **d**: M = $SiMe_3$)

Whereas the "kinetic" enolates (**1**) of 2-methylcyclohexanone are known to be formed as $\geq$90% pure substances upon treatment of the ketone with hindered bases, such as $KN(SiMe_3)_2$[2] and $LiN(Pr\text{-}i)_2$,[4] direct generation and characterization of the "thermodynamic" enolates (**2**) as $\geq$90% pure substances do not appear to have been previously reported.[5,6] In particular, the regioselectivity reported in the literature for the conversion of 2-methylcyclohexanone into the silyl enol ether **2d** via **2b** has ranged from 37 to 67%.[7] On the other hand, we have recently found that both **1a** and **2a** generated as described above can be cleanly converted into 90-95% regioisomerically pure methyl and neryl substituted products[3,8] (Scheme 1).



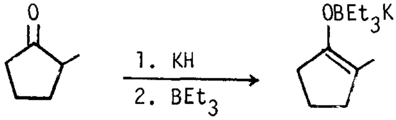
Scheme 1

These results prompted us to examine the regiochemistry of 1a and 2a by the silylation technique, and we observed essentially the same 90-95% regioselectivity in each silylation (Scheme 1).

Noting that, unlike 1b and 2b, both 1a and 2a dissolve readily in THF, their ^{1}H and ^{13}C NMR spectra were recorded in THF-d$_8$. The ^{1}H NMR spectrum of 1a shows a doublet at 0.91 ppm for the 6-methyl protons. Although less definitive, a multiplet centered at 3.26 ppm may tentatively be assigned to the alkenyl proton. The "thermodynamic" enolate 2a displays a singlet at 1.56 ppm for the 2-methyl group. The ^{13}C NMR spectra of 1a shows two major signals at 97.85 and 160.32 ppm for the alkenyl carbon atoms, while the alkenyl carbon signals for 2a appear at 103.13 and 151.47 ppm. A long pulse delay (4 sec) was used to minimize complication due to variable T$_1$s. Under these conditions, the ratio of the intensities of two alkenyl carbon signals remains within the 0.9-1.1 range. Whereas the ratio of 2a to 1a in the KH reaction remained virtually constant over 2 days at ambient temperature (room temperature = ca. 22°C, NMR probe temperature = ca. 35°C), that in the $KN(SiMe_3)_2$ reaction increased with time and reached the 90/10-95/5 range over 24 h at the NMR probe temperature, but it did not change appreciably thereafter. Similar results were obtained by GLC examination of the silylated products, and these results are summarized in Table 1. On the basis of these data we conclude that, under these conditions, the 90/10-95/5 mixture of 2a and 1a represents an equilibrium mixture. We have also found that the use of an excess of BEt_3 (B/K = 2-3) is effective in retarding isomerization of 1a to 2a (Table 1). Thus, when 3 equiv of BEt_3 were used, a 91:9 mixture of 1a and 2a was isomerized into an 83:17 mixture over 24 h at room temperature whereas the use of 1.25 equiv of BEt_3 isomerized the same 91:9 mixture into a 48:52 mixture of 1a and 2a during the same period. This facile isomerization might be due to the presence of $HN(SiMe_3)_2$ which could complex with BEt_3 to regenerate free potassium enolate. If so, such a reaction should be retarded through complexation of $HN(SiMe_3)_2$ with an excess of BEt_3.

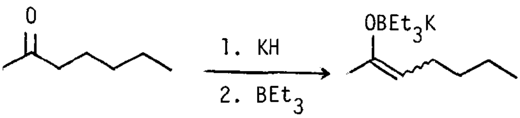
Since the ratio of 2a to 1a agrees well with that of 2d and 1d as well as those of the 2-substituted and 6-substituted products, we may now conclude that the reactions of 1a and 2a shown in Scheme 1 are all highly regiospecific (95-100%). While direct determination of the exact regioisomeric purities of 1b and 2b remains difficult, the fact that both 1a and 2a are obtained as 90-95% pure species suggests that their regioisomeric purity must not be much lower than 90-95%. This in turn suggests that, if the reported figures of 37-67% for the regioisomeric purity of 2d were accurate, conversion of 2b to 2d might possibly involve considerable regiochemical scrambling.

To probe the scope of the $KH-BEt_3$ procedure as well as to determine the regioselectivity in some other cases, we subjected 2-methylcyclopentanone and 2-heptanone to the $KH-BEt_3$ reaction and obtained 4 and 5 as 91 and 85% regioisomerically pure species, as judged by ^{13}C NMR. The alkenyl carbon signals for 4 appear at 103.26 and 157.02 ppm, while those of its regioisomer appear at 92.94 and 165.51 ppm. Likewise, the alkenyl carbon signals for 5 appear at 101.31, 101.56, 155.19, and 155.57 ppm, the E/Z ratio being roughly 1/1. The regioisomer of 5 displays the corresponding signals at 81.30 and 167.46 ppm. The regioselectivity in the formation of 4 determined by the silylation technique is 93%.



4

(91% 2-Me)



5

(85% 2-heptenyl)

It should be pointed out here again that the regioselectivity figures reported in the literature for the generation of potassium enolates either corresponding to or similar to 4 and 5 are only ca. 80 and ca. 60%, respectively.[5b] In summary, apart from the somewhat puzzling discrepancy between the regioselectivity figures for potassium enolates reported in the literature and those for enoxyborates reported here, the $KH-BEt_3$ procedure promises to provide a highly regioselective route to "thermodynamic" enolates that are not only readily soluble in organic solvents, e.g., THF, but also capable of reacting regiospecifically with electrophiles.

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Table 1 Regiochemical Stability of "Kinetic" and "Thermodynamic" Potassium Enoxyborates **1a** and **2a**

	1a/**2a**[a]		
Time, h	1.05 eq $KN(SiMe_3)_2$ 1.25 eq BEt_3	1.05 eq $KN(SiMe_3)_2$ 3 eq BEt_3	1.05 eq KH 1.25 eq BEt_3
0	90/10[b]	91/9	7/93[c]
2	82/18	89/11	5/95
6	79/21	88/12	4/96
12	69/31	85/15	5/95
24	48/52	83/17	4/96
48	18/82	—	—
60	7/93	—	—

[a] The reagents indicated are those used to generate the potassium enoxyborates. [b] The **1a**/**2a** ratio determined by ^{13}C NMR was 92/8. [c] The **1a**/**2a** ratio determined by ^{13}C NMR was 9/91.

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