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A HIGHLY SELECTIVE METHOD FOR α-ALKYLATION OF KETONES *VIA* POTASSIUM ENOXYTRIALKYLBORATES

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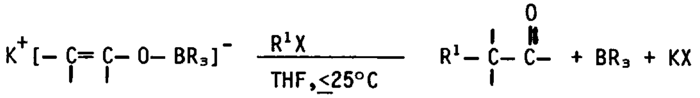
Despite numerous recent developments in the area of chemistry of enolates,[1] it still remains difficult, in many cases, to control regiochemistry, stereochemistry and the number of carbon-carbon bonds formed in the reaction of enolates with carbon electrophiles.

Rapid scrambling between enolate derivatives and carbonyl compounds appears to be largely responsible for these difficulties. One logical approach is to make use of enol derivatives containing highly covalent metal-oxygen bonds. Indeed, various reactions of silyl enol ethers[2] and enoxydialkylboranes[3] have provided solutions to some of the above-mentioned difficulties. Unfortunately, however, these new methodologies are not useful in the alkylation of carbonyl compounds, since neither silyl enol ethers nor enoxydialkylboranes are reactive toward typical alkyl halides, e.g., MeI.

We now wish to report that potassium enoxytrialkylborates, readily obtainable by treating potassium enolates with trialkylboranes, undergo a remarkably selective reaction with alkyl halides according to Eq 1.

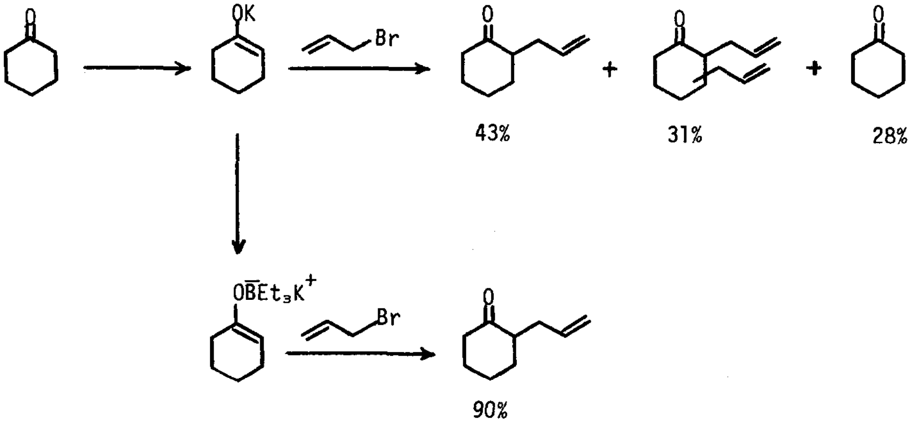


$$K^+[-\underset{|}{C}=\underset{|}{C}-O-BR_3]^- \xrightarrow[\text{THF},\leq 25^\circ\text{C}]{R^1X} R^1-\underset{|}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}- + BR_3 + KX \qquad (1)$$

Typically, cyclohexanone was sequentially treated with 1.05 equivalents of potassium hydride[4] in THF at room temperature, triethylborane (1.25 equiv., room temp.), and allyl bromide (1.5 equiv., room temp.). After 15 min, examination of the reaction mixture by GLC and ^{1}H NMR indicated that 2-allylcyclohexanone was formed in 90% yield as the only product as shown in Eq 2. Neither cyclohexanone nor diallylcyclohexanone was present in any more than trace amount.

When the reaction was carried out in the absence of triethylborane, the yield of 2-allylcyclohexanone was only 43%, and the diallylated products were formed in 31% combined yield along with a trace amount of triallylated products. The latter results observed in the absence of triethylborane are strikingly similar to those observed by

Ganem[5] in the reaction of allyl bromide with the 2-cyclohexenone-potassium tri-sec-butylborohydride reaction product (mono : di : non = 55:30:15). We have also carried out the alkylation reaction using tri-sec-butylborane instead of triethylborane. The mono- and diallylated products were formed in 46 and 26% yields, respectively. These results indicate that the course of the alkylation is critically dependent on the trialkylborane used in the reaction. Indeed, our spectroscopic study[6] reveals that, whereas the complexation between potassium cyclohexenolate and triethylborane is complete, only a partial formation of potassium cyclohexenoxytri-sec-butylborate is observed between potassium cyclohexenolate and tri-sec-butylborane. Thus, the 2-cyclohexenone-potassium tri-sec-butyl-borohydride reaction product obtained by Ganem[5] must also be a mixture of potassium cyclohexenolate, tri-sec-butyl-borane and the corresponding borate complex.



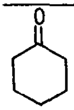
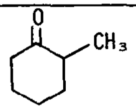
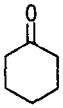
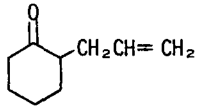
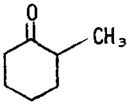
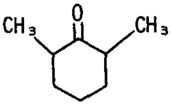
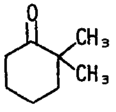
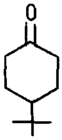
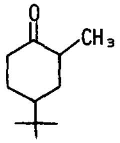
(2)

Selection of the metal gegenion of the base used in this reaction is also of critical importance. We have previously found that typical lithium enolates, such as those obtained from acetophenone and cyclohexanone, do not form the corresponding enoxytrialkylborates even with unhindered trialkylboranes, such as triethylborane.[7] Thus, although the possible intermediacy of lithium enoxytrialkylborates has been inferred in a few alkylation studies,[8] we believe that these authors have dealt with mixtures of lithium enolates and boranes. Only in one reported case, significantly improved results were observed by running the methylation of sodium cyclohexenolate in the presence of triethylborane,[8b] and this may indeed represent the first bona fide example of the alkylation of enoxytrialkylborates. However, the success has been limited to this example only.

While it is clear that the presently reported reaction involves preformed potassium enoxytrialkylborates, it is not possible to rule out the possibility of observing a reaction of potassium enolates present in minute equilibrium concentrations.

Irrespective of the precise mechanism, however, the present reaction promises to provide a highly selective procedure for alkylation of ketones, as indicated by the results summarized in Table.

Table α-Alkylation of Ketones via Potassium Enoxytrialkylborates

Ketone	Alkyl Halide	Monoalkylated Product (% Yield)[a]
	ICH_3	 (95)
	$BrCH_2CH{=}CH_2$	 (90)
 [b]	ICH_3	 (80) +  (6)[c,d]
	ICH_3	 (95)
$PhCOCH_3$	ICH_3	$PhCOCH_2CH_3$ (98)
$PhCOCH_3$	$I(CH_2)_5CH_3$	$PhCO(CH_2)_6CH_3$ (68)[e]
$PhCOCH_3$	$BrCH_2CH{=}CH_2$	$PhCO(CH_2)_2CH{=}CH_2$ (94)[f]
$PhCOCH_3$	$BrCH_2C{\equiv}CH$	$PhCO(CH_2)_2C{\equiv}CH$ (63)[g,h]
$PhCOCH_3$	$BrCH_2Ph$	$PhCO(CH_2)_2Ph$ (90)[f]

[a] Unless otherwise mentioned, the alkylation reactions were carried out by the addition of 1.5 equiv. of alkyl halide to a THF solution of 1.25 equiv. of Et_3B and 1.0 equiv. potassium enolate at $\leq 25°$. The reaction mixture was stirred for 1 to 3 hr before treatment with aq. $NaOH/H_2O_2$ followed by GLC analysis using internal standards. Yields are based on starting ketones. Only traces, if any, of the starting ketones and the di- and polyalkylated products were detected by GLC. [b] The potassium enolate was prepared by the addition of the ketone to a THF solution of potassium bis(trimethylsilyl)amide at -78°C as reported in Ref. 4. [c] 9% of 2-methylcyclohexanone was detected. [d] The 2,6-dimethylcyclohexanone was a mixture of 75% cis and 25% trans isomers. [e] The reaction time was 18 hr, and 30% of $PhCOCH_3$ was detected. [f] 7% of $PhCOCH_3$ was detected. [g] No trace of the corresponding allene was detected by isolation and ^1H NMR analysis. [h] The reaction time was 18 hr, and 36% of $PhCOCH_3$ was detected.

The following observations are particularly noteworthy. 1) In the reaction of the "kinetic"[4] enoxytrialkylborate derived from 2-methylcyclohexanone, the 2,6-2/2-isomer ratio is 93/7. As the reaction of 2-methylcyclohexanone with potassium bis(trimethylsilyl)amide is known to give a 95/5 mixture of potassium 6- and 2-methylcyclohexenolates,[4] the overall alkylation process must be highly regiospecific (ca. 98%). 2) No difficulty was encountered in achieving a highly selective mono-alkylation with n-hexyl iodide, which reacted with the corresponding lithium or potassium enolate to give far less satisfactory results. 3) Finally, the reaction of propargyl bromide proceeds without being accompanied by allylic rearrangement. It thus promises to provide a facile route to 1,4- and 1,5-dicarbonyl compounds.

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