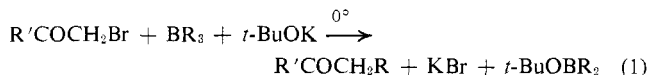


Reaction of Organoboranes with α -Bromo Ketones under the Influence of Potassium *t*-Butoxide in Tetrahydrofuran. A New Technique for the α Alkylation of Ketones

Sir:

We wish to report that α -bromo ketones, such as phenacyl bromide and α -bromocyclohexanone, react readily with organoboranes under the influence of potassium *t*-butoxide in tetrahydrofuran to produce the corresponding α -alkyl derivatives (1). This new



technique avoids the concurrent formation of polyalkyl derivatives which is characteristic of alkylation with sodamide and alkyl halides¹ and therefore provides a valuable new synthetic route to such alkyl derivatives.

It has long been known that ketones containing enolizable hydrogen in the α position can be alkylated by treating the ketone with sodamide or a similar strong base and an appropriate alkyl halide.^{1,2} A major difficulty with this reaction is the fact that it is difficult to control the reaction to bring about the introduction of a single alkyl group. The reaction frequently proceeds to the production of a wide range of the possible alkylated products, and frequently chemical methods must be utilized to isolate a single product from the mixture.¹

This had led to the use of blocking groups,³ on the one hand, and to the use of enamines,⁴ on the other, to control such alkylation.

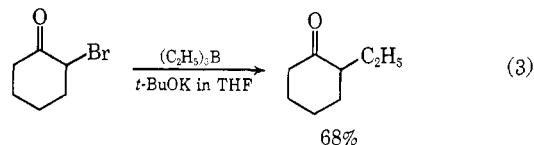
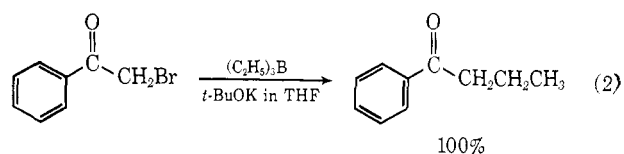
Our recent success in achieving the alkylation of ethyl bromoacetate⁵ and ethyl dibromoacetate⁶ with organoboranes encouraged us to explore the possibility of achieving a similar alkylation of α -bromo ketones. Unfortunately, the procedure developed for the bromo esters proved to be unsatisfactory for the α -bromo ketones. Thus, treatment of a 1:1 molar mixture of phenacyl bromide and triethylborane with potassium *t*-butoxide in *t*-butyl alcohol at 0° resulted in only a 25% yield of *n*-butyrophenone.

This result was not unexpected since α -bromo ketones, such as phenacyl bromide and α -bromocyclohexanone, are highly sensitive to the action of strong bases. Thus they undergo condensations readily, they undergo the Favorski rearrangement,⁷ and in some instances they undergo elimination easily.⁸

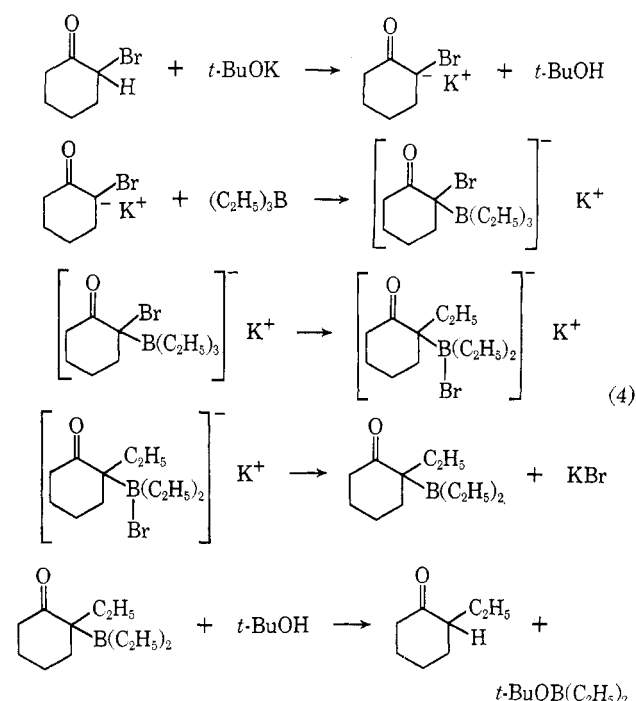
Fortunately, these side reactions do not appear to be a major factor when potassium *t*-butoxide in tetrahydrofuran is used.

At 0° phenacyl bromide reacts practically instantly with triethylborane to give an essentially quantitative

yield of *n*-butyrophenone (2). The reaction of α -bromocyclohexanone is much slower, but even this proceeds relatively smoothly to give 68% of α -ethylcyclohexanone in approximately 12 hr⁹ (3). Presum-



ably the reaction involves the formation of an α -bromo carbanion and reaction of the carbanion with the triethylborane, followed by rearrangement of the intermediate⁵ (4).



It is somewhat amazing that α -bromocyclohexanone can apparently exist in some form (possibly as the potassium salt, as shown) for a number of hours, while undergoing the relatively slow reaction resulting in the formation of the alkyl derivative. For this synthesis to be convenient, there is need for a simple preparation of the α -bromo ketones. Fortunately, the reaction of cupric bromide with ketones in ethyl acetate-chloroform appears to provide such a procedure.¹⁰

We explored the applicability of various organoboranes in this new alkylation procedure with phenacyl bromide. There was no difficulty in utilizing tri-*n*-butylborane or tri-*n*-decylborane (5). However, branched-chain organoboranes, such as tri-*sec*-butylborane and triisobutylborane, failed to react. Evidently the reaction is sensitive to the steric environment of the boron atom. Fortunately, we have discovered a

(1) For a summary of alkylation reactions of ketones with sodamide and other strong bases see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 184-204.

(2) L. Claisen, *Ber.*, **38**, 697 (1905); A. Haller and E. Bauer, *Ann. Chim. (Paris)*, **28**, 373 (1913).

(3) W. S. Johnson, *J. Am. Chem. Soc.*, **65**, 1317 (1943).

(4) G. Stork, A. Brizzolara, H. Landerman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(5) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **90**, 818 (1968).

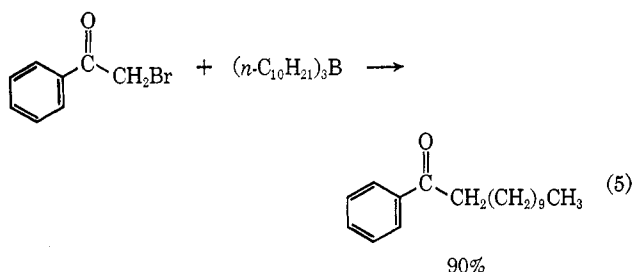
(6) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **90**, 1911 (1968).

(7) A. Favorski and V. Boshowski, *J. Russ. Phys. Chem. Soc.*, **46**, 1098 (1914).

(8) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 162.

(9) The reaction is essentially complete in 1 hr at 25°.

(10) L. C. King and G. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964). This procedure was modified to permit carrying the reaction out at room temperature, as described in this communication.



means of circumventing this difficulty.¹¹ This solution is currently under study and will be reported shortly.

Representative results are summarized in Table I.

Table I. Reaction of Representative α -Bromo Ketones with Organoboranes under the Influence of Potassium *t*-Butoxide

Bromo ketone ^{a,b}	Organoborane	R ₃ B, mmol	Temp, °C	Time, hr	Yield, ^c %
Phenacyl bromide	Triethyl	10	0	0.1	93
	Triethyl	20	0	0.1	100
α -Bromocyclohexanone	Triethyl	10	0	5.0	50
		20	0	0.25	24
				2.0	35
				5.0	50
				12	68
				48	68
α -Bromocyclohexanone	Triethyl	20	25	1.0	55
				<i>d</i>	71
Phenacyl bromide	Tri- <i>n</i> -butyl	10	0	0.1	61
		10	0	0.1	75 ^e
		20	0	0.1	93
	Tri- <i>sec</i> -butyl	20	0	0.1	0
	Triisobutyl	20	0	0.1	0
	Tri- <i>n</i> -decyl	20	0	0.1	90

^a 10.0 mmoles. ^b 10.0 mmoles of potassium *t*-butoxide was used, except where otherwise indicated. ^c Glpc analysis. The yield is based on the bromo ketone. ^d After 24 hr, the analysis revealed a yield of 58% with 10% of residual α -bromo ketone. Addition of 2.0 mmoles of potassium *t*-butoxide raised the product to 71%. ^e Simultaneous addition of the phenacyl bromide and the base to the organoborane.

The synthesis of α -bromocyclohexanone is illustrated by the following procedure. A 1-l. round-bottom flask was equipped with a mechanical stirrer and water condenser. Cupric bromide (223 g, 1.0 mol) was placed in the flask together with 500 ml of a 1:1 mixture of ethyl acetate and chloroform containing 49 g (0.5 mol) of cyclohexanone. The system was attached to a water aspirator, and a pressure sufficient to achieve gentle refluxing of the solvent was maintained. Stirring was then started and the evolution of hydrogen bromide began immediately. After 1 hr, the disappearance of the black cupric bromide was almost complete. The solution was filtered to remove the white precipitate of cuprous bromide and extracted with three 100-ml portions of a saturated solution of sodium bicarbonate. Removal of the solvent and distillation under reduced pressure gave 53 g (60%) of α -bromocyclohexanone, bp 66° (2 mm). A slight red color in the product could be removed by crystallization from pentane at -72°.

The following procedure for the conversion of α -bromocyclohexanone into 2-ethylcyclohexanone is representative. A 50-ml round-bottom flask equipped

(11) E. F. Knights and H. C. Brown, *J. Am. Chem. Soc.*, **90**, 5280, 5281, 5283 (1968).

with septum inlet and magnetic stirring bar was flushed with nitrogen and maintained under a static pressure of the gas. Twenty milliliters of a 1 *M* solution of triethylborane in tetrahydrofuran was injected into the flask followed by 1.78 g (10 mmoles) of α -bromocyclohexanone. The flask was placed in an ice bath and stirring was initiated. Ten milliliters of a 1 *M* solution of potassium *t*-butoxide in tetrahydrofuran was then added dropwise over a period of 5 min. The solution was analyzed periodically for 2-ethylcyclohexanone by glpc, and a yield of 68% after 12 hr of reaction was established.

The same procedure was followed for the experiments with phenacyl bromide. In this case analysis of the reaction mixture immediately following completion of the addition of the potassium *t*-butoxide indicated the reaction was already complete.

Considerable study has been devoted to the halogenation of ketones.¹² In cases where the α -bromo ketone is readily accessible, the present procedure promises to provide a simple means for introducing alkyl substituents without the concurrent formation of polyalkylated materials and, in addition, promises to make it possible to introduce substituents of structural types that cannot now be introduced by the older alkylation procedures. We are currently exploring these possibilities.

(12) H. O. House, ref 1, pp 144-156.

(13) National Science Foundation Postdoctorate Fellow at Purdue University, 1967-1968.

Herbert C. Brown, Milorad M. Rogić, Michael W. Rathke¹³

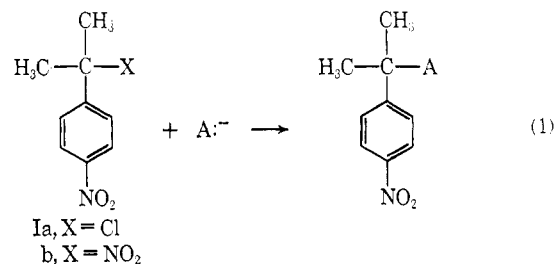
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Received August 30, 1968

New and Facile Substitution Reactions at Tertiary Carbon. The *m*-Nitrocumyl System

Sir:

A new type of substitution at a tertiary carbon in which the chlorine of *p*-nitrocumyl chloride (Ia) undergoes replacement by a variety of anions (eq 1) was described in 1967.¹ More recently, a striking set of



reactions in which the aliphatic nitro group of α ,*p*-dinitrocumene (Ib) is smoothly displaced by a number of anions (eq 1, X = NO₂) was reported.² The facility with which Ia and Ib react (eq 1) is in sharp contrast to the lack of reactivity exhibited by cumyl chloride (IIa) and α -nitrocumene (IIb) toward the various anions.^{1,2} Similarly, *p*-nitrobenzyl chloride, when treated with the lithium salt of 2-nitropropane,

(1) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.*, **89**, 725 (1967).

(2) N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *ibid.*, **89**, 5714 (1967).