Tetrahedron Letters,Vol.24,No.27,pp 2737-2740,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

COMPARISON OF SYN DEHYDROHALOGENATIONS FROM TRANS-1-BROMO-2-CHLOROCYCLOALKANES PROMOTED BY COMPLEX BASE AND BY POTASSIUM TERT-BUTOXIDE

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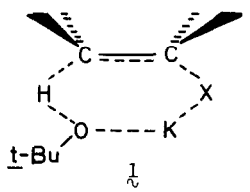
Summary: Compared with t-BuOK-t-BuOH, syn eliminations from trans-1-bromo-2-chlorocycloalkanes (C_4-C_8) induced by $NaNH_2$-NaO-t-Bu in THF are rapid, exhibit greater propensity for dehydrochlorination and show little sensitivity to ring size of the dihalocycloalkane.

Base-solvent combinations of t-BuOK in t-BuOH, benzene or toluene facilitate 1,2-eliminations of HX which proceed with syn stereochemistry.[1] For these associated bases,[1] transition state 1 has been invoked to explain the enhanced propensity for syn eliminations from alkyl and cycloalkyl halides and arenesulfonates as well as from analogous substrates which contain



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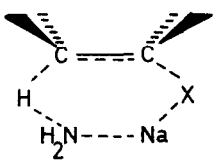

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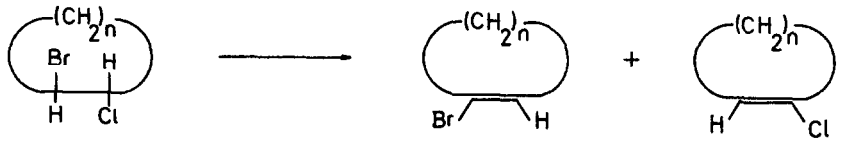
activating β-aryl or β-halogen groups.

Caubére has reported remarkable syn dehydrobrominations in reactions of the "complex base" of $NaNH_2$-NaO-t-Bu in THF with trans-1,2-dibromocycloalkanes which produce high yields of 1-bromoalkenes.[2] Transition state 2 was proposed for these complex base induced syn eliminations.[2,3] We have observed that reactions of complex base with trans-1-bromo-2-chlorocyclohexane favor dehydrochlorination over dehydrobromination.[4]

In view of the similarity between postulated transition states 1 and 2, a direct comparison of syn eliminations from common substrates promoted by complex base and by associated t-BuOK should be enlightening. Results from the reactions of complex base and of t-BuOK-t-BuOH with a series of trans-1-bromo-2-chlorocycloalkanes (3a-e)[5] which are reported herein reveal large differences in reactivity and regioselectivity for the two base-solvent combinations.



Reactions of 3a,b,d,e with $NaNH_2$-NaO-t-Bu in THF at room temperature were conducted[8] under conditions which provide the products of kinetic control.[3] The heterogeneous reaction mixtures were sampled and analyzed by GLPC after 15, 30, 45, 60 and 120 minutes to determine the length of time required for consumption (<1% remaining) of the substrate. The reaction times for completion and the elimination product proportions at completion are listed in the Table.

Reactions of 3a-e with 0.50 M t-BuOK-t-BuOH at 50°C were sampled and analyzed by GLPC for unreacted substrate after 0.5, 1, 2, 3, 4 and 5 days.[9] For 3b-d the reactions were incomplete even after 5 days. Reaction times and elimination product proportions at the termination of the reactions are recorded in the Table.

For complex base-promoted syn eliminations from trans-1,2-dihalocycloalkanes, the t-BuONa serves only to activate the effective base species $NaNH_2$.[3] Therefore, this comparison of the two base-solvent combinations involves the same concentrations of dihalocycloalkane and effective base. The much greater reactivity of $NaNH_2$-NaO-t-Bu in THF compared with t-BuOK-t-BuOH is striking (Table). This is particulary evident for eliminations from 3b,c promoted by complex base which are complete after reaction for 2 h at room temperature, but are very incomplete after reaction with t-BuOK-t-BuOH at 50°C for 5 days. Clearly complex base is the reagent of choice amongst base-solvent combinations which facilitate syn eliminations for inducing dehydrohalogenation of trans-1,2-dihalocycloalkanes.

For reactions of 3a-e with t-BuOK-t-BuOH, dehydrobromination predominates over dehydrochlorination with the 1-bromocycloalkene comprising approximately 15% of the elimination product in all cases except one (Table). For 3c only 5% of the dehydrochlorination product is observed. The change to complex base enhances the proportion of dehydrochlorination product (relative to that for dehydrobromination) for every dihalocycloalkane examined. Thus even though transition states such as 1 are proposed for syn eliminations promoted by t-BuOK-t-BuOH,[1] it appears that base counterion-leaving group interactions (which favor removal of the normally poorer,[10,11] but more electronegative, leaving group[4]) are stronger in transition state 2 for complex base-induced elimination.

In reactions of the dihalocycloalkanes with complex base, dehydrochlorination either predominates over (for 3a) or is essentially equal to (for 3b,c,d) dehydrobromination for all substrates except one. Only for 3e is the dehydrobromination product dominant. This suggests a possible weaking of base counterion-leaving group interactions in transition states involving trans-1-bromo-2-chlorocyclooctane. We propose that this results from steric interactions between the activated sodium amide surface and portions of the cyclooctane ring.

For syn eliminations from 3a-e induced by t-BuOK, the ring size of the dihalocycloalkane exerts a pronounced influence upon reactivity. Based upon the yield data, the apparent reactivity order is 3a>>3e>3d>3b≈3c. This variation in reactivity probably results from different

dihedral angles for syn eliminations from the various dihalocycloalkanes. In comparison, the reactivity differences for eliminations from 3a-e promoted by $NaNH_2$-NaO-t-Bu in THF at room temperature are very small indeed. This contrasting effect of ring size upon reactivity reveals further differences between transition states 1 and 2. For the complex base-promoted syn eliminations, the insensitivity of reactivity to ring size variation indicates transition states with limited double bond character. High basicity of the amide ion should produce highly carbanionic E2 transition states[1] which have little double bond development.

In summary, substantial differences are evident for transition states 1 and 2. The latter appears to possess stronger base counterion-leaving group interactions, less double bond development and more ElcB character than the former.

Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

References and Notes

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(2) P. Caubére, Acc. Chem. Res., 7, 301 (1974).
(3) A. P. Croft and R. A. Bartsch, J. Org. Chem., in press.
(4) J. G. Lee and R. A. Bartsch, J. Am. Chem. Soc., 101, 228 (1979).
(5) The trans-1-bromo-2-chlorocycloalkanes 3b,c,e were available from previous studies.[4,6] Substrates 3a,d were prepared by reactions of the corresponding cycloalkenes with N-bromoacetamide and aqueous HCl.[7]
(6) J. G. Lee, Doctoral Dissertation, Texas Tech University, 1978.
(7) Concentrated HCl (100 ml) was diluted with an equal volume of ice-water and chilled to -10°C. The cycloalkene (0.40 mol) and 55.2 g (0.40 mol) of N-bromoacetamide were added simultaneously over a 30 min period to the well-stirred reaction mixture at -5 to -10°C. After an additional 30 min of stirring, the organic layer was separated and extracted twice with Et_2O. The combined extracts were washed with 10% $NaHCO_3$ solution and then water and were dried over anhydrous Na_2SO_4. After evaporation of the solvent in vacuo, 3a was isolated by preparative GLPC (Anal. Calcd for C_4H_6BrCl: C, 28.35; H, 3.57. Found: C, 28.54; H, 3.61) and 3d was purified by distillation (116-118°C/18 mm. Anal. Calcd for $C_7H_{12}BrCl$: C, 39.74; H, 5.72. Found: C, 39.94, 5.69).
(8) Under nitrogen, 9.8 mmol of powdered $NaNH_2$ (Fisher) was weighed into a 25 ml round bottomed flask fitted with a reflux condenser. To the top of the condenser was attached a T-tube through which a slow flow of nitrogen was passed during the course of the reaction. Then t-BuOH (4.9 mmol) and 8.0 ml of dry THF were added and the mixture was stirred magnetically for 1 h. The dihalocycloalkane (3.3 mmol) was added to the stirred heterogeneous base-solvent combination at room temperature. The reactions were monitored by periodic removal of 2 µl aliquots which were analyzed by GLPC. When this analysis indicated that the dihalocycloalkane had been consumed, the reaction mixture was poured into 70 ml of ice-water in a 100 ml volumetric flask. The reaction flask was rinsed with a small amount of Et_2O. The rinsings and additional Et_2O (total of 30 ml) were added to the ice-water mixture. Following the addition of an appropriate internal standard and shaking, the flask was allowed to stand overnight in a refrigerator. The organic layer was then analyzed by GLPC.
(9) A 0.50 M solution of t-BuOK in t-BuOH was prepared by reaction of clean potassium metal with t-BuOH under nitrogen. Into a 5 ml volumetric flask was placed 1.6 mmol of the dihalocycloalkane and the flask was filled to the mark with 0.50 M t-BuOK in t-BuOH. After shaking, the flask was suspended in a 50°C constant temperature bath. Periodic removal of 2 µl samples and GLPC analysis were used to measure consumption of the dihalocycloalkane. Following the reaction period, the mixture was poured into ice-water, worked up and analyzed by GLPC by the same procedure which was utilized for the complex base promoted eliminations.
(10) R. A. Bartsch and J. F. Bunnett, J. Am. Chem. Soc., 90, 408 (1968).
(11) J. F. Bunnett in "Survey of Progress in Chemistry," Vol 5, A. F. Scott (Ed.), Academic press, New York, 1969, pp 53-93.

Table. Base Promoted Syn Eliminations from trans-1-Bromo-2-chlorocycloalkanes

Ring size of dihalocycloalkane	$NaNH_2$-NaO-t-Bu in THF at room temperature			t-BuOK in t-BuOH at 50°C		
	Reaction time for completion	Relative proportion of 1-bromocycloalkene, %[a,b]	Yield of 1-halocycloalkenes, %[b]	Reaction time for completion	Relative proportion of 1-bromocycloalkene, %[a,b]	Yield of 1-halocycloalkenes, %[b]
4	1 h	55	88	1 day	15	88
5	2 h	52	86	5 days[c]	17	7[c]
6	2 h	65[d]	87[d]	5 days[c]	5	3[c]
7	1 h	46	92	5 days[e]	16	70[c]
8	0.75 h	35	100	5 days	14	90

[a]Relative proportion of 1-bromocycloalkene in the total 1-halocycloalkenes. [b]Estimated uncertainty is 0.03 X the stated value or 2% whichever is larger. [c]Incomplete reaction with much unreacted dihalocycloalkane present. [d]Data are from Reference 3. [e]Incomplete reaction with some unreacted dihalocycoalkane present.

(Received in USA 9 November 1982)