Tetrahedron Letters Vol. 21, pp 4317 - 4320 0040-4039/80/1101-4317$02.00/0

RETENTION OF CONFIGURATION IN THE OPENING OF 2-ARYLCYCLOPROPYL BROMIDES BY POTASSIUM ACETATE/18-CROWN-6 IN DIMETHYL SULFOXIDE

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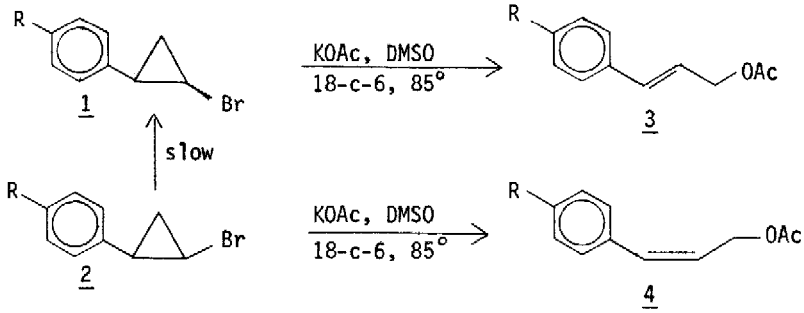
SUMMARY: E and Z 2-phenylcyclopropyl bromides react with the title reagents to yield E and Z cinnamyl acetates respectively. No reaction is observed when halide nucleophiles or other aprotic solvents are used suggesting a novel mechanistic role for the acetate ion.

There continues to be interest in the outcome of forcing cyclobutyl and cyclopropyl halides and alkylsulfonates to react with nucleophiles under S_N2 conditions. Molecular orbital calculations predict either retention of configuration[1,2] or inversion[3] to be favored in these small rings. Experimental tests of these predictions have been reported and in each case retention was initially reported[4a,5a] and later corrected to inversion.[4b,5b,6]

We wish to report the E and Z 2-phenylcyclopropyl bromides (1a,2a) react with the powerful nucleophile, potassium acetate in the presence of 18-crown-6,[7] in dry DMSO to produce E and Z cinnamyl acetate (3a,4a) respectively.



a: R=H, b: R=CH_3

This is the first isolation of a Z cinnamyl product from the opening of a phenylcyclopropyl compound. Both the Z and E isomers of 2-phenylcyclopropyl bromides[8a] and chlorides[8b] undergo solvolytic ring opening in acetic acid to give exclusively 3a. In addition, pyrolysis

of Z 2-phenylcyclopropyl acetate at 450° produces primarily 3a, no 4a product was reported.[9]

The known phenylcyclopropyl bromides[8a] were prepared by tri-n-butyltin hydride reduction[10] of the corresponding geminal dibromide produced by phase-transfer reaction of styrene with bromoform.[11] For 1b and 2b, p-methylstyrene was prepared from 1-(p-tolyl)ethanol by dehydration with $KHSO_4$.[12] Z and E isomers[13] were separated by distillation through a 1 meter Teflon spinning band column or by preparative gas chromatography on an 8% FFAP column.

In a typical experiment, 5 mMole of 1a was stirred, under nitrogen, with 10 mMole of dried potassium acetate and 0.5 mMole of 18-crown-6 (Aldrich) in 10 ml of dry DMSO at 85° for 18 hours. The reaction mixture was poured into water and extracted with dichloromethane. The organic phase was concentrated on the rotary evaporator to about one milliliter and taken up in 50 ml of diethyl ether which was filtered through ten grams of silica gel in a fritted glass funnel. Removal of ether gave a product mixture, free of 18-crown-6 and DMSO, containing 1.5 mM unreacted 1a (30%) and 3.3 mM 3a (66%) based on GC analysis (XE-60, 125°). Pure 3a, isolated by preparative GC, had NMR, IR and mass spectra identical to authentic material prepared in 92% yield from E cinnamyl alcohol (Eastman) by the method of Duyk.[14] The stereochemistry of allyl acetates 3a,b,4a,b was assigned from NMR coupling coupling constants[15] and chemical shift values of the vinyl protons.[16]

Because of the heterogeneous nature of these reactions, rate constants were not determined; however under pseudo first-order conditions, kinetic plots of the reactions of 1a and 1b were linear through the first 40% of reaction. Based on initial slopes of these plots, 1b reacts 2.3 times faster than 1a (Hammet $\rho+$ value -1.2). Solvolyses of E 2-arylcyclopropyl tosylates in acetic acid give $\rho+$ values of -1.75[17] and 1-arylcyclopropyl tosylates give $\rho+$ values of -4.31.[17] Reaction of 1a to 3a gave no evidence for the formation of 2a, 4a or other products as judged by GC and NMR. Compound 2a reacts at one third the rate of 1a to give a mixture of 78% 4a and 22% 3a. Because small amounts of 1a can be detected during the reaction of 2a we believe that isomer 3a is arising via slow isomerization of 2a to 1a.

Any proposed mechanism for these reactions must be consistent with the following observations: 1) Compounds 1 and 2 in the presence of 18-crown-6 did not react with KOAc, KCl or KI within 72 hours in the following solvents: Acetonitrile (55°), Benzene (75°), Toluene (110°). 2) Exo and endo 7-bromo- and 7-chloro-norcarane did not react with KOAc or KI in these solvents or in DMSO. 3) The 2-phenylcyclopropyl chlorides react much slower than compounds 1a and 2a.[18] 4) 1a Is recovered unchanged in 92% yield after 24 hours at 85° in DMSO in the presence of 18-crown-6; in particular no evidence for isomerization to cinnamyl bromide under these conditions was found; 5) 2-Phenylcyclopropyl acetates may be distilled[19] at 85° (.25 Torr) and are stable at 147° in sodium acetate-acetic acid solutions.[17] 6) A mixture of 1b and 2b when heated to 85° with 18-crown-6 in DMSO 1 molar in $KClO_4$, recovered after 96 hours, showed no isomerization to allylic bromides, although slow isomerization of 2b to 1b occurred. 7) Addition of two equivalents of the radical anion trap, m-dinitrobenzene,[20] did not affect the reaction of 1a to E-cinnamyl acetate. 8) The radical anions formed from 1a or 1b by electron transfer are reported to interconvert but not to open to cinnamyl products.[21] 9) Preliminary

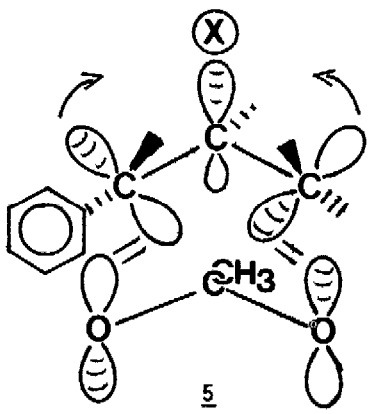
experiments with 2-n-butylcyclopropyl bromide with KOAc and 18-crown-6 in DMSO indicate the production of a complex mixture of heptenyl acetates at a rate slower than that of 2a.

We believe these observations support a concerted mechanism where acetate attack on carbon 3 of the ring is simultaneous with C_2-C_3 bond rupture and the departure of the bromide ion. However this does not explain the high nucleophilicity of acetate compared with halides in this system. Liotta[7] found little variation in rate among acetate, halides and cyanide as nucleophiles in reaction with benzyl tosylate in the presence of 18-crown-6 in acetonitrile.

Under our standard reaction conditions 1a and 2a with KCl and 18-crown-6 in DMSO are largely unreacted after 18 hours. By GC on both SE-30 and XE-60 columns no phenylcyclopropyl chlorides[22] and only a small amount of cinnamyl chloride were detected. Cinnamaldehyde, a conceivable oxidation product of cinnamyl chloride in DMSO, was not detected.

We believe these observations support a concerted mechanism in which attack of nucleophile is simultaneous with carbon-carbon bond rupture and departure of the bromide ion. Specifically we propose a disrotatory solvolysis of the cyclopropyl halide in which the only solvation available to the cation is acetate which captures it before E/Z isomerization can occur.

If the HOMO of acetate interacts with the LUMO of the incipient allyl cation as shown in 5 (similar to a Cope or Claisen rearrangement) then the special reactivity of acetate is rationalized.



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Cyclopropane diazonium ions have recently been shown to undergo stereospecific disrotatory ring opening to allylic alcohols in aqueous sodium bromide solutions.[23] Minor products (1-8%) from these reactions are the unopened cyclopropyl bromides formed with inversion of configuration at carbon. Internal displacement of diphenyl sulfide from a tertiary cyclopropylsulfonium salt to yield a spiro epoxide also proceeds with inversion.[24] Although these examples leave no doubt that nucleophilic substitutions may occur on cyclopropyl centers with inversion, the activation energy is evidently so great that except in very special cases the reactions take alternate routes as illustrated here.

Acknowledgement: We thank the donors of the Petroleum Research Fund administered by the American Chemical Society and the Eastern Illinois University Council on Faculty Research for support of this work, Ms. P.A. Stal for technical assistance, and a referee for helpful comments.

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    3a: δH_1=6.62, δH_2=6.26, δH_3=4.63, $J_{1,2}$=16Hz, $J_{1,3}$<0.5Hz.
    3b: δH_1=6.60, δH_2=6.21, δH_3=4.60, $J_{1,2}$=17.2Hz, $J_{1,3}$=0.8Hz.
    4a: δH_1=6.63, δH_2=5.78, δH_3=4.75, $J_{1,2}$=12.8Hz, $J_{1,3}$=1.6Hz.
    4b: δH_1=6.61, δH_2=5.80, δH_3=4.81, $J_{1,2}$=12.4Hz, $J_{1,3}$=1.6Hz.

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(Received in USA 27 December 1980)