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MESUT BOZ

HAFİZE ÇALIŞKAN

ÖMER ZAİM

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Silver Ion-Assisted Ring Expansions in Different Solvent Systems

Mesut BOZ, Hafize ÇALIŞKAN, Ömer ZAİM*
Department of Chemistry, Trakya University, 22030, Edirne-TURKEY
e-mail: omerzaim@trakya.edu.tr

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Several ring expansion products carrying vinylic bromo functionality were synthesized by opening of the geminal dibromobicyclo[n.1.0]alkanes ring. Dibromocarbene was formed from bromoform and potassium tert-butoxide in hexane. Its reaction with various cyclic alkenes was the resultant dibromobicyclo[n.1.0]alkanes. Then, opening was performed using $AgNO_3$ in various solvent systems, such as acetic acid/DMSO, acetic acid/DMF, CH_3OH/acetone, and H_2O/DMF.

Key Words: Carbene, bicyclic compound, ring opening, ring expansion, vinylic halide.

Introduction

Carbenes that contain uncharged divalent carbons are useful and quite reactive intermediates in organic chemistry. These intermediates can easily be added to alkenes to give substituted cyclopropane, which leads to ring expansion by opening. There are numerous reviews about the synthesis and use of dihalocyclopropanes.[1–5] Dibromocarbene, which simultaneously adds to double bonds, is made from bromoform and potassium tert-butoxide. Two geminal halogen substituents on a cyclopropane ring results in the shortening of the adjacent bonds and a lengthening of the opposite bond.[6,7] As a result, the C_2-C_3 bond is generally broken during ring-opening reactions. In spite of that fact, the products formed by the addition of dibromocarbene to 5- or 6-membered rings are stable under normal conditions. If it is added to smaller rings, such as a 4-membered one, the adduct becomes unstable and undergoes a ring-opening reaction, even below room temperature.[8] Recently, it was reported that the addition product of dibromocarbene and cyclobutene rearranges to the ring opening product at –30 °C.[8] Promotion of ring expansion of *gem*-dibromobicyclo[n.1.0]alkanes with the silver ion represents a useful approach for the construction of medium-sized rings. The ring opening generally leads

*Corresponding author

to cyclic structures with trans geometry when performed in the presence of strong nucleophiles.[9] Loozen et al. observed that reactions of *gem*-dibromobicyclo[n.1.0]alkanes with silver tosylate in acetonitrile gave 2-bromo-3-tosyloxycycloalk-1-en. When silver nitrate was used as the reagent, nitrate esters on 3-positions were produced. The product was 2-bromo-3-tert-butyloxycycloalk-1-en[9] when tert-butanol was used as the solvent. The opening reaction of *gem*-dibromocyclopropane with silver cyanate was used for the synthesis of the Amaryllidacea alkaloids, crinasiadine, N-methylcrinasiadine, and trisphaeridine.[10] A practical, high-yielding, inexpensive, and mild method for the synthesis of 2-halo-2-cycloalkenols was reported without using silver salts, by simple heating in DMSO.[11] Opening reactions of the *gem*-dibromocyclopropane ring with silver acetate in acetic acid were used for the synthesis of α-alkylidene-β-lactams. Hydrolysis of acetate esters was followed by bromination, and condensation of an allylic bromo compound with benzylamine afforded a secondary amine, and then the insertion of carbon monoxide to the secondary amine gave corresponding α-alkylidene-β-lactams.[12] *Gem*-dibromocyclopropane ring opening with sodium acetate in glacial acetic acid was used for the preparation of acetate esters in order to investigate chemoselectivity in palladium-catalyzed reactions of 2-bromoallyl esters.[13] Balcı and Jones used *gem*-dibromocyclopropane ring opening to produce 1,2-cycloheptadiene and 1,2-cyclohexadiene, so as to examine their structures.[14] The relationship between ring size and the geometry of 2-bromo-2-cycloalkenyl acetates that were prepared from dibromocyclo[n.1.0]alkanes and silver acetate was demonstrated by Ziffer et al.[15] Using these observations, we first tried the ring-opening reactions of *gem*- dibromobicyclo[n.1.0]alkanes with silver nitrate in an acetic acid/DMF solvent system and then other solvent systems were examined for comparison.

Experimental

General

Column chromatography was performed on silica gel (0.063-0.200 mm) with EtOAc/Hexane mixtures. TLC was performed on silica gel 60F-254 precoated sheets. IR spectra were taken with Shimadzu IR 470 or ATI Unicam Mattson 1000 Fourier Transform IR spectrophotometers. ^{1}H NMR and ^{13}C NMR spectra were obtained in deuteriochloroform solution with a Varian Mercury Plus 300 MHz spectrometer. Mass spectra were measured with a Thermo Trace GC Ultra DSQ II instrument, with electron impact at 70 eV. Only isolated yields were reported.

All chemicals and solvents were purchased from Aldrich, Merck, and Fluka, and were used without additional purification.

General Procedure for Preparation of a Dibromocyclopropane Ring from Alkenes

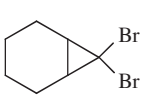
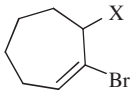
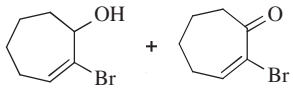
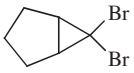
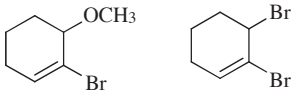
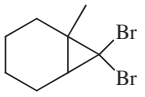
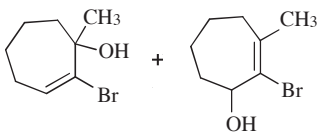
In 10 mL of dry hexane, 10 mmol of cycloalkene and 13 mmol of potassium tert-butoxide were mixed and placed in a 50-mL round-bottom flask. A dropping funnel containing 13 mmol of bromoform in 5 mL of dry hexane was fitted onto one of the necks of the flask. The other neck was connected to an N_2 source. The flask was placed in a salted ice bath and maintained between –5 °C and –10 °C, while the bromoform solution was added dropwise to a magnetically stirred mixture. After the addition was completed, the flask was removed from the cooling bath and the mixture was stirred at room temperature for 2 h. Then, a small amount of water

was added and the mixture was poured into brine. The organic phase was separated and the aqueous phase was washed several times with hexane. The combined organic phase was dried over $CaCl_2$ and filtered, and then the hexane was evaporated. The remaining material was pure enough to use in the ring-opening reaction, according to the ^{1}H NMR spectrum.

General Procedure for Opening Reactions of the *gem*-Dibromocyclopropane Ring

Into a 25-mL round-bottom flask was placed 1.1 mmol of $AgNO_3$ in a mixture of 5 mL DMF and 1 mL of acetic acid. Into a magnetically stirred mixture was added 1 mmol of dibromocyclopropane containing the related compound. The mixture was stirred for 24 h at 60 °C. The reaction was monitored by TLC. The mixture was poured into 50 mL of water after the reaction was completed. The aqueous phase was extracted with 10 mL of ether, 3 times. The combined ether phases were neutralized with saturated sodium bicarbonate solution and dried over calcium chloride and filtered, and ether was evaporated. The residue was purified by column chromatography. Structures were determined by IR, ^{1}H NMR, and ^{13}C NMR, GC-MS spectra.

Table 1. Geminal dibromobicyclo[n.1.0]alkanes and products.

Reagent	***Products***
 **(2)[a]**	 X=OCHO **(3)** X=O_2CCH_3 **(4)** X=OH **(5)**
 **(2)[b]**	 **(5)** + **(6)**
 **(8)[c]**	 **(9)** **(10)**
 **(12)[d]**	 **(13)** + **(14)**

[a]DMF-AcOH, [b]DMSO-AcOH, [c]CH_3OH-Acetone, [d]H_2O-DMF

2-Bromo-2-cycloheptenyl Format (3)

Yield: 7%; IR 2927, 1735, 1635, 1450, 856, and 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 8.14 (s, 1H), 6.54 (t, J = 6.74 Hz, 1H), 5.67-5.69 (m, 1H), and 1.56-2.34 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$)δ165.4, 140.7, 110.0,

86.7, 28.9, 28.5, 25.9, and 23.8; MS (EI) m/z (%) = no molecular ion, 176.0 (5), 174 (5), 139 (M^+ – Br, 100), 111 (98), and 93 (92).

2-Bromo-2-cycloheptenyl Acetate (4)

Yield: 17%; IR 3055, 2927, 1738, 1635, 1244, 863, and 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 6.41 (t, J = 6.74 Hz, 1H), 5.52-5.56 (m, 1H), and 1.56-2.33 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$)δ 170.3, 137.7, 124.2, 75.7, 30.1, 28.3, 28.2, 26.0, and 23.8; MS (EI) m/z (%) = no molecular ion, 153 (M^+ – Br, 40), 111 (100), and 93 (20).

2-Bromocyclohept-2-enol (5)

Yield: 30%; IR 3464, 3055, 2927, 1635, 1450, 1086, 860, and 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 6.31 (t, J = 6.74 Hz, 1H), 4.45 (m, 1H), and 1.60-2.24 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$)δ134.7, 130.1, 75.7, 32.6, 28.2, 26.1, and 23.4; MS (EI) m/z (%) = no molecular ion, 192.0 [(M^+ + 2)-H, 6], 190.0 (M^+ – H, 6), 173.9 (40), 171.9 (40), 111 (88), and 93 (100).

2-Bromo-2-cycloheptanone (6)

Yield: 12%; IR 2960, 1676, 1603, 1449, 854, and 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.26 (t, J = 6.60 Hz, 1H), 2.66 (t, J = 1.80 Hz, 2H), 2.38 (q, 2H), and 1.10-1.90 (m, 4H);^{13}C NMR (75 MHz, $CDCl_3$)δ196.7, 147.9, 127.4, 41.5, 29.5, 25.0, and 21.4; MS (CI) m/z (%) = 191.1 (M^+ + 2, 100), 189.1 (M^+, 100), and 111.2 (40).

1-Bromo-6-methoxy-1-cyclohexene (9)

Yield: 21%; IR 2960, 1638, 1436, 860, and 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 6.21 (dd, J = 3.52, 4.69 Hz, 1H), 3.72 (t, J = 3.37 Hz, 1H), 3.42 (s, 3H), and 1.51-2.16 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$)δ133.8, 122.8, 78.9, 57.6, 28.5, 28.1, and 17.2; MS (CI) m/z (%) = 193.1 (M^+ + 2, 50), 191.1 (M^+, 50), and 111.2 (100).

1,6-Dibromo-1-cyclohexene (10)

Yield: 13%; IR 2944, 1628, 1436, 851, and 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 6.48 (dd, J = 3.22, 5.30 Hz, 1H), 5.51 (broad s, 1H), and 1.51-2.26 (m, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 115.3, 81.2, 29.4, 27.7, and 16.8; MS (CI) m/z (%) = 243.2 (M^+ + 4, 0.4), 241.1 (M^+ + 2, 0.4), 239.1 (M^+ , 0.4), 161.1 (100), 159.1 (100), 81.1 (6), and 79.1 (6).

2-Bromo-1-methylcyclohept-2-en-1-ol (13)

Yield: 18%; IR 3424, 2944, 1638, 1446, 1270, and 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 4.50 (m, 1H), 1.18–2.35 (m, 8H), and 1.88 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$)δ 136.6, 132.6, 76.3, 32.3, 28.0, 27.0, 25.2, and 21.6; MS (CI) m/z (%) = 207.1(M^+ + 2, 5), 205.1 (M^+, 5), 189.1 (100), 187.1 (100), 125.2 (44), and 107.2 (25).

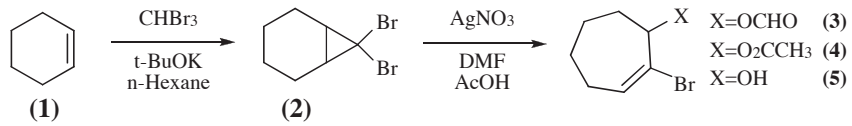
2-Bromo-3-methylcyclohept-2-en-1-ol (14)

Yield: 31%; IR 3440, 2944, 1641, 1459, 1241, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)δ 6.22 (t, J = 6.74 Hz, 1H), 1.51-2.41 (m, 8H), and 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 125.9, 75.8, 37.0, 34.0, 27.5, 25.0, and 24.3; MS (CI) m/z (%) = 207.1 (M^+ + 2, 5), 205.1 (M^+, 5), 189.1 (100), 187.1 (100), 125.2 (44), and 107.2 (33).

Results and Discussion

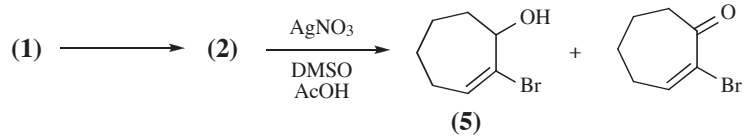
Strained *gem*-dibromocyclopropane rings that were formed by the addition of dibromocarbene to cycloalkenes gave synthetically useful vinylic halogen compounds after opening. Expansion reactions were tried in different solvent systems and then the products were compared. In most of these works, solvent attacks to forming carbocation during the reaction, due to its nucleophilic character, were noted. We tried a dibromo cyclopropane ring-opening reaction to make larger rings in singly nucleophilic solvent systems.

The ring-opening reaction of 7,7-dibromobicyclo[4.1.0]heptane **(2)** in an acetic acid/DMF solvent system yielded 2-bromo-2-cycloheptenyl formate **(3)**, 2-bromo-2-cycloheptenyl acetate **(4)**, and 2-bromo-2-cycloheptenol **(5)**.



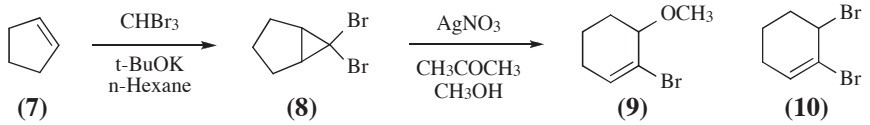
Scheme 1.

The same reaction was tried in an acetic acid/DMSO solvent system and gave 2 different products (2-bromo-2-cycloheptenol **(5)** and 2-bromo-2-cycloheptanone **(6)**).



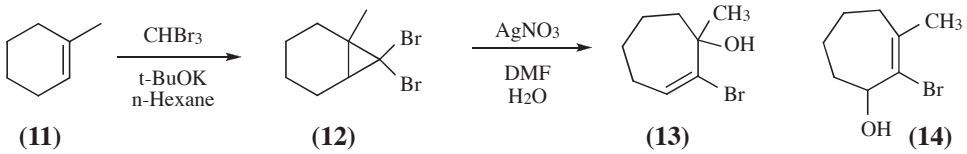
Scheme 2.

Opening 6,6-dibromobicyclo[3.1.0]hexane (**7**) in a methanol/acetone solvent system resulted in 1-bromo-6-methoxy-1-cyclohexene **(9)**[16] and 1,6-dibromo-1-cyclohexene **(10)**.



Scheme 3.

Another solvent system (H_2O/DMF) was also used for ring-opening reactions of the dibromocyclopropane ring that was synthesized from branched alkenes and only gave the alcohol derivatives, 2-bromo-1-methylcyclohept-2-en-1-ol **(13)** and 2-bromo-3-methylcyclohept-2-en-1-ol **(14)**.



(11) **(12)** **(13)** **(14)**

Scheme 4.

Conclusion

In conclusion, ring-opening reactions of *gem*-dibromobicyclo[n.1.0]alkanes in various solvent systems yielded several ring expansion products, depending on the nucleophilic character of the solvent. We expected mainly one product that would correspond to the nucleophilic solvents from the reactions, but the actual outcome was quite complicated. The acetic acid/DMF solvent system surprisingly yielded a formate ester and an alcohol, in addition to an expected acetate ester. The acetic acid/DMSO solvent system also unexpectedly gave an alcohol and a ketone, but not a desired acetate ester.

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