Notes

A Direct Retro-Barbier Fragmentation

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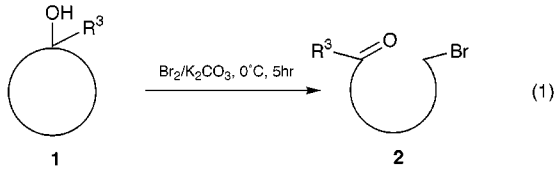
The metal mediated carbon−carbon bond formation between alkyl halides and carbonyl compounds, the Barbier-type reaction, is a fundamental reaction in organic chemistry.[1] Such a reaction has played the key role in synthesizing numerous important biological and abiological compounds. In contrast to the well-recognized and extensively studied Barbier reaction, the reversed reaction (the retro-Barbier reaction) has been explored much less due to the lack of a simple and efficient method in carrying out such transformations (Scheme 1). On the other hand, among many potential applications, such a reaction of cyclic alcohols would provide ω-haloketones. These compounds are important intermediates in many syntheses. Herein we report a direct retro-Barbier fragmentation reaction of cyclic tertiary alcohols that proceeds under mild conditions to generate ω-bromoketones in high yields (eq 1).

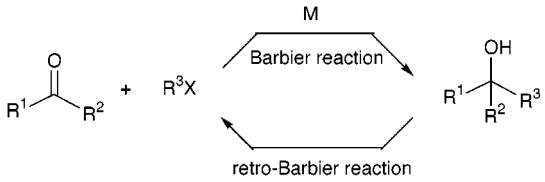


(1)

1 **2**

Previously, it has long been known that the decomposition of tertiary alkyl hypochlorites at a high temperature or by photolysis led to the carbon−carbon bond cleavage products.[2] The decomposition was proposed[3] as a radical chain reaction.[4] Alternatively, cyclic secondary and tertiary alcohols were converted into hypoiodites with $HgO-I_2$, and a subsequent photolysis of the hypoiodites led to the β-scission of the alkoxy radical intermediates.[5] The formation of ω-bromoketones was also reported in moderate yields by treating tertiary alcohol with base and bromine followed by photolysis of the intermediate with sunlight.[6] On the other hand, alkoxy radicals with γ-stannyl groups undergo fragmentation reactions to generate alkenes under mild conditions.[7] To our knowledge, a simple and direct (without photolysis or thermolysis of the intermediates) retro-Barbier type reaction has not been reported.

Scheme 1



To start our investigation, we reacted **1a** (1 equiv) with bromine (10 equiv) in chloroform (10 mL) in the presence of potassium carbonate (15 equiv) for 3 h at 0 °C. TLC analysis of the reaction mixture clearly showed the quantitative conversion of the starting material into a new compound. Subsequently, ^{1}H NMR measurement of the crude reaction mixture showed an essentially pure product. The cleanness of the reaction was further confirmed by ^{13}C NMR measurement of the crude reaction mixture. Subsequently, many cyclic tertiary alcohols were treated with bromine and potassium bicarbonate, and in all cases the corresponding fragmentation products were obtained in high yields (Table 1). The use of methyl, ethyl, propyl, or phenyl as the side chain did not affect the reaction process significantly. However, an inseparable mixture of products was obtained when the side chain was a butyl group. The change of the ring size resulted in only minute changes in the product formations. The reaction also proceeded when less bromine (5 equiv) was used; however the conversion was less than 50% within the same reaction period when the amount of bromine was reduced to 3 equiv. The reaction is also successful in methylene chloride or acetonitrile. In the latter case, however, a small amount of further α-bromination of the product was observed. No significant difference was observed with potassium carbonate, so-

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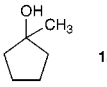
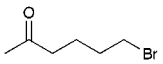
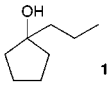
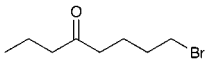
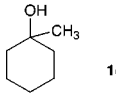
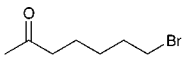
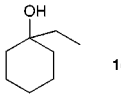
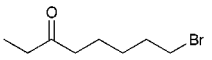
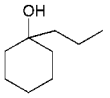
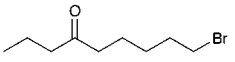
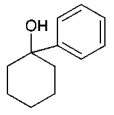
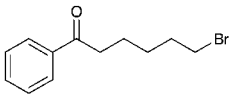
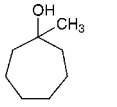
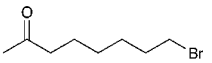
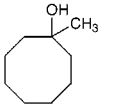
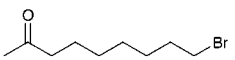
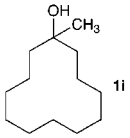
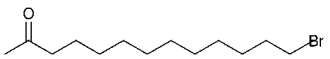
Table 1. Formation of ω-Bromoketones *via* Retro-Barbier Fragmentation[a]

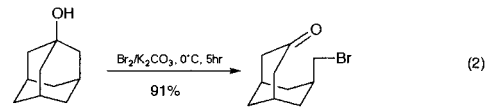
entry	substrate (1)	product (2)	yield (%)
1	 1a	 2a	97
2	 1b	 2b	90
3	 1c	 2c	95
4	 1d	 2d	80
5	 1e	 2e	89
6	 1f	 2f	96
7	 1g	 2g	92
8	 1h	 2h	83
9	 1i	 2i	90

[a] All reactions were carried out on 1−3 mmol scales with 1 equiv of the alcohol, 6 equiv of potassium carbonate, and 5 equiv of bromine at 0 °C for 5 h.

dium carbonate, potassium hydroxide, or sodium hydroxide as the base. When $KHCO_3$ was used as the base or when less base (compared with bromine) was used, unspecified polymeric material was formed together with the desired product. No reaction was observed with $NaHCO_3$ being the base.

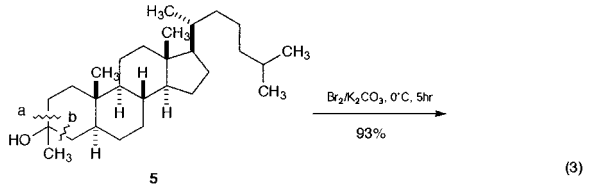
It is worthwhile to mention that the cleavage of the branched alkyl group was not detected initially by ^1H NMR of the crude product. A subsequent direct GC/MS analysis of the reaction mixture of 1-*n*-propylcyclohexanol showed a very small amount of cyclohexanone (<5%), resulting from the cleavage of propyl group. The origins of the regioselective ring opening in this reaction remain unclear. Further study of the reaction in chloroform revealed that a large amount of CCl_3Br, due to halogenation of the $CHCl_3$ solvent, was generated during the reaction. This observation suggests that the bromine is largely consumed in a radical chain halogenation reaction of the solvent. Schreiner et al.[8] recently reported an efficient and highly regioselective iodination of unactivated aliphatic hydrocarbons which was driven by a direct free-radical reaction. The triiodomethyl radical, $\cdot CI_3$, was believed to be the radical chain carrier and the cause of the high selectivity in the reaction, which prevented polyiodination and other typical radical side reactions. These interesting findings could probably be used to explain the high selectivity of observed fragmentation in the present reaction. However, the reaction also proceeds when either CH_2Cl_2 or CH_3CN was used as the solvent, which seems that a radical process may not be necessary for the reaction. A detailed study for the reaction mechanism is still under investigation.

When an admantane derivative **3** was reacted under the same reaction conditions, a [3,3,1] bridged product **4** was generated (eq 2). The mildness of the conditions for fragmentation and the effectiveness of the reaction were demonstrated by the reaction of a cholesterol derivative (eq 3); again a nearly quantitative reaction was observed

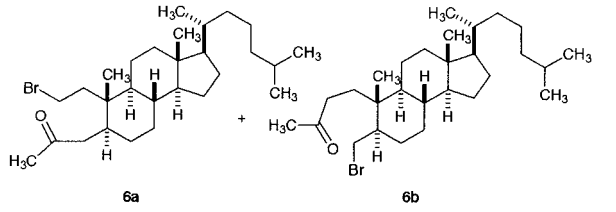


(2)

3 **4**



5 (3)



6a **6b**

~50 : 50

in generating a ca. 1:1 mixture of two isomers (**6a** and **6b**) resulting from two prime C−C cleavages (a and b). The drawback of the reaction is the requirement of an excess amount of bromine and base. Presently, we are investigating the mechanism, the origin of the high selectivity in carbon−carbon bond cleavage, and synthetic applications of this direct retro-Barbier reaction.

Experimental Section

Commercially available chemicals were purchased from Aldrich and were used directly as received. Flash chromatography employed E. Merck silica gel (Kiesegel 60, 230−400 mesh) purchased from Scientific Adsorbents. Elemental analyses were carried out at the Center of Instrumental Facility of Tulane University.

A General Procedure for the Fragmentation Reaction. To a solution of 1-methylcyclopentanol (300 mg, 3 mmol) in 10 mL of chloroform was added potassium carbonate (2.48 g, 6 × 3 mmol). The reaction mixture was stirred at 0 °C for 10 min, and bromine (2.4 g, 5 × 3 mmol) was then added. After stirring at 0 °C for 5 h, TLC analysis showed the completion of the reaction.

(8) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Fokin, A. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2786.

The mixture was washed with saturated aqueous sodium thiosulfate solution and water, dried over magnesium sulfate, filtered through a short path of silica gel (*: flash chromatography on silica gel was used for purification in some examples), and concentrated in vacuo to give compound **2a** (521 mg, yield 97%).

8-Bromooctane-4-one (2b). FTIR (film): 1713, 1366, 1249, 1122 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): $\delta = 3.35$ (t, $J =$ 6.4 Hz, 2H), 2.41 (t, $J = 7.2$ Hz, 2H), 2.34 (t, $J = 7.2$ Hz, 2H), 1.80 (m, 2H), 1.68 (m, 2H), 1.54 (m, 2H), 0.86 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): $\delta = 210.5$, 44.7, 41.5, 33.3, 32.1, 21.2, 17.2, 13.7; GC/MS: *m*/*z* (% base peak) 209 (^{81}Br $M^+ + 1$, 2), 207 (^{79}Br $M^+ + 1$, 3), 163 (21), 135 (36), 127 (90), 71 (100), 43 (90). Anal. Calcd for $C_8H_{15}OBr$: C, 46.40; H, 7.30. Found: C, 46.53; H, 6.97.

***endo*-7-(Bromomethyl)bicyclo[3.3.1]nonan-3-one (4).** FTIR (film): 1717, 1465, 1381, 1355, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): $\delta = 3.06$ (d, $J = 7.04$ Hz, 2H), 2.41 (m, 2H), 2.25 (dd, $J =$ 11.3, 5.6 Hz, 4H), 2.05 (m, 2H), 1.79 (m, 2H), 1.52 (m, 1H), 0.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): $\delta = 212.3$, 50.2, 39.5, 32.9, 32.0, 28.4, 28.4; GC/MS (50 ev): *m*/*z* (% base peak) 151 ($M^+ -$ Br, 26), 150 (100), 95 (48), 79 (57), 39 (57). Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.64; H, 6.37. Found: C, 51.56; H, 6.13.

(3*R*,3a*R*,5a*S*,6*S*,7*S*,9a*R*,9b*S*)-Dodecahydro-6-[2-bromoethyl]-3a,6-dimethyl-3-[(1*R*)-1,5-dimethylhexyl)]-7-[2-oxopropyl]-1*H*-benz[*e*]indene (6a) and (3*R*,3a*R*,5a*S*,6*R*,7*R*,-9a*R*,9b*S*)-Dodecahydro-7-(bromomethyl)-3a,6-dimethyl-3-[(1*R*)-1,5-dimethylhexyl)]-6-[3-oxobutyl]-1*H*-benz[*e*]indene (6b) (mixture). FTIR (film): 1699, 1652, 1456, 1436, 1235 cm^{-1}; ^1H NMR (for CH_2Br) ($CDCl_3$, 400 MHz, ppm): $\delta = 2.99$(t, $J = 6.9$ Hz, 2H) (**6a**), 3.60(dd, $J = 10.0$, 2.6 Hz, 2H) (**6b**); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): $\delta =$ (**6a** + **6b**): 208.8, 208.6, 56.6, 56.5, 56.2, 56.2, 47.7, 47.6, 45.6, 44.9, 42.2, 42.2, 40.6, 40.1, 39.8, 39.5, 39.2, 37.8, 36.6, 36.4, 36.1, 35.7, 35.7, 35.2, 35.0, 31.4, 31.4, 31.0, 30.2, 29.5, 28.2, 28.2, 28.1, 28.1, 28.0, 26.2, 24.2, 23.8, 22.8, 22.6, 21.6, 20.8, 18.6, 16.2, 16.2, 11.9. Anal. Calcd for $C_{28}H_{49}OBr$: C, 69.83; H, 10.25. Found: C, 69.71; H, 9.88.

Acknowledgment. We are grateful to LEQSF and the NSF CAREER Award program for partial support of our research.

Registry Numbers (provided by author): 1-Methylcyclopentanol, [1462-03-9]; 1-propylcyclopentanol, [1604-02-0]; 1-methylcyclohexanol, [590-67-0]; 1-ethylcyclohexanol, [1940-18-7]; 1-propylcyclohexanol, [5445-24-9]; 1-phenylcyclohexanol, [1589-60-2]; 1-methylcycloheptanol, [3761-94-2]; 1-methylcyclooctanol, [59123-41-01]; 1-methylcyclododecanol, [32400-09-2]; 1-butylcyclopentanol, [1462-97-1]; 1-adamantanol, [768-95-6]; 6-bromo-2-hexanone, [10226-29-6]; 7-bromo-2-heptanone, [50775-02-5]; 8-bromo-3-octanone, [2146-62-5]; 9-bromo-4-nonanone, [54314-60-2]; 6-bromo-1-phenyl-1-hexanone, [82777-11-5]; 8-bromo-2-octanone, [60099-86-7]; 9-bromo-2-nonanone, [52330-02-6]; 13-bromo-2-tridecanol, [96562-67-3]; 3-methylcholestanol, [1251-59-8][1251-58-7].

Supporting Information Available: Results of characterization by ^1H NMR, ^{13}C NMR, FT-IR, and elemental analysis for all fragmentation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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