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Reductive Ring Opening of Cyclopropyl Ketones with Samarium (II) Diiodide

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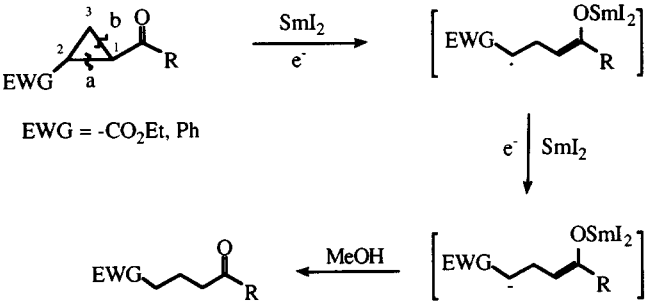
ABSTRACT

Functionalized cyclopropyl ketones have been found to undergo facile reductive cyclopropane ring opening with samarium (II) diiodide in the presence of a proton source. These reactions were exceedingly rapid, taking place in most cases at −78°C under neutral conditions. An ester group substituted at the C_2 position of the cyclopropane ring played an important role in the ring opening of cyclopropyl ketones.



SCHEME 1

INTRODUCTION

Since the pioneering work of Kagan [1] in 1980, samarium diiodide (SmI_2) has shown its versatile synthetic utility in organic synthesis [2]. Samarium (II) diiodide, a strong one-electron transfer reagent, is an exceedingly useful reagent for the reduction of many organic functional groups. One of the most representative reactions is a reduction of carbonyl groups to alcohols. This reduction of carbonyl groups occurs via a ketyl radical anion. It has been well established that an adjacent ketyl radical anion center can induce the opening of strained rings such as cyclopropane, epoxide and cyclobutane. Lithium-ammonia [3], zinc-zinc dichloride [4], photochemical excitation [5], and tributyltin hydride [6] have also been used for the reductive ring opening of cyclopropyl ketones. However, the use of the $Zn/ZnCl_2$ system is limited to aryl-substituted cyclopropyl ketones and requires drastic conditions.

During the course of our own research, a cleavage of cyclopropyl ketones using samarium (II) diiodide was published by other workers [7]. The yields were low perhaps due to the instability of a carbanion intermediate. It is well known that the β-carbon atom (C_2) of a cyclopropyl ketone develops a considerable degree of carbanion character during the reductive cleavage with lithium in liquid ammonia [3]. Therefore, if a functional group which can stabilize a carban ionic center is introduced at C_2 of a cyclopropyl ketone, it can be expected that the ring opening occur in a regioselective fashion.

We have examined the activation of C_1—C_2 bond cleavage of a cyclopropane ring by introducing an electron-withdrawing group at the C_2 atom (Scheme 1). Thus, we are able to report an effective method for a regioselective reductive ring opening of cyclopropyl ketones using SmI_2.

RESULTS AND DISCUSSION

A series of functionalized cyclopropyl ketones were reacted with 2 equiv of SmI_2 in THF at −78°C to

Dedicated with love and admiration to Professor Yao-Zeng Huang on the occasion of his eightieth birthday.

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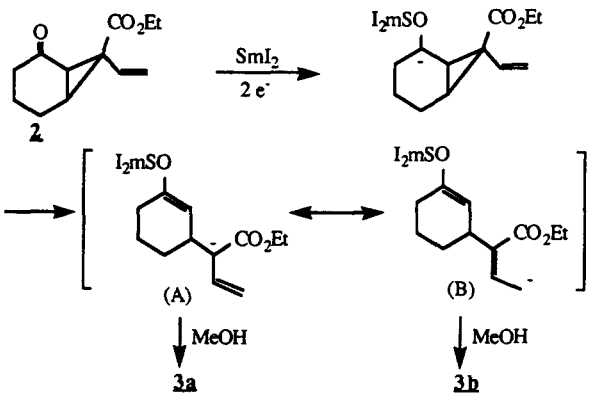


SCHEME 2

give the ring-opened products in good yields. It is noteworthy that the reactions are both regio- and chemo-selective. The product formed by path **a** (as shown in Scheme 1) was obtained exclusively and both ketone and ester moieties, which are sensitive toward other reductants, remained without being destroyed under the mild reaction conditions. Reactions took place rapidly at −78°C within 10 minutes. The results obtained are listed in Table 1. The cyclopropyl ketones **1** [8], **2** [9], and **4** [10] were readily obtained according to published procedures. When the lithium dienolate anion derived from ethyl 2-bromocrotonate was added to cyclohexenone, the expected cyclopropyl ketone **2** was obtained as a mixture of exo/endo isomers (60/40) [9]. These isomers were separated and isolated in pure form, and then each was reacted with 2 equiv of SmI_2. For the endo isomer, the ring-opened products **3a** and **3b** were obtained in 85% yield in a ratio of 3:1 (entry 2). The ratio was 2:1 in the case of the exo isomer. The structures of **3a** and **3b** were distinguished by ^1H NMR (300 MHz) spectroscopy, and the ratio of **3a/3b** was determined by capillary GC. The products **3a** and **3b** are probably formed from the anion intermediate (A) ↔ (B) in MeOH, as shown in Scheme 2. Formation of **3a** is kinetically favored and **3b** is thermodynamically favored. On the other hand, for the phenyl-substituted cyclopropyl ketone, a pinacol coupling product was formed as the main product, together with the ring-opened product that was obtained in 25% yield (entry 3 of Table 1).

A SmI_2-promoted reduction of α,β-unsaturated esters has also been reported [1]. On the application of the SmI_2-promoted 1,4-reduction of α,β-unsaturated esters, we have also found that the conjugated cyclopropane **5** was reductively cleaved on treatment with SmI_2 to give the ring-opened product in excellent yields under the mild conditions (Scheme 3).

The carbon-carbon bond cleavage appears to take place via an intermediate **6** which was described in the case of the reduction of vinyloxirane reported by Molander *et al.* [11]. The reactions were completed within a few minutes by addition of the substrates dissolved in THF/MeOH to SmI_2 in THF at −78°C. As described in the ring opening of cyclopropyl ketones, it is clear that the ester group substituted at C_2 of the cyclopropane ring plays an important role in the ring opening of the conjugated vinyl cyclopropanes. The results obtained are summarized in Table 2.

In summary, the methodology described above provides an effective reductive ring opening of cyclopropyl ketones and conjugated cyclopropanes by the one-electron transfer reagent SmI_2. The presence of an ester group substituted on the C_2 carbon atom of the cyclopropane ring is an important controlling factor for these ring-opening processes. The scope and mechanism of these reactions are under investigation.

EXPERIMENTAL

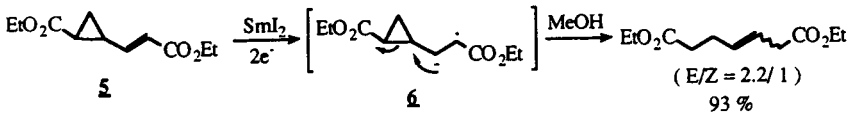
Solvents and commercial reagents were purified by conventional methods before use. Column chromatography and TLC were performed on silica gel 70–230 mesh and silica gel F_{254} plates, respectively (both from E. Merck). Nuclear magnetic resonance spectra were recorded in $CDCl_3$ solution with a Bruker AM-300 spectrometer operating at 300.13 MHz (^1H) and at 75.47 MHz (^{13}C) with a Varian T-60A, FA-80A spectrometer. Infrared spectra were taken on a Perkin-Elmer Model 253B and a Bomem MB-100 FT-IR spectrometer. Mass spectra were obtained on a Hewlett Packard GC/MS 5985B instrument. GLC analyses were performed on a varian 3700 gas chromatograph using an FID detector.

Reductive Ring Opening of Cyclopropyl Ketone **2a**

A solution of **2a** (104 mg, 0.5 mmol) in THF (2 mL) and t-BuOH (1 mL) was added at −78°C to a solution of SmI_2 (1 mmol) in THF (5 mL). The resultant brown mixture was stirred for 10 minutes at −78°C, the reaction quenched at this temperature by addition of 10% aqueous K_2CO_3 solution, and then warmed to room temperature. The aqueous phase was extracted with Et_2O (5 mL × 3), and the combined extracts were dried over $MgSO_4$, concentrated in vacuo, and then chromatographed on a column of silica gel (eluent; Et_2O:n-hexane = 1:2) to give the product (89 mg, 85% yield) as a mixture of **3a** and **3b** isomers. The isomer ratio **3a/3b** was 3:1, as determined by capillary GC analysis.

Spectral Data

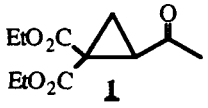
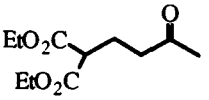
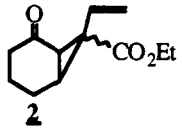
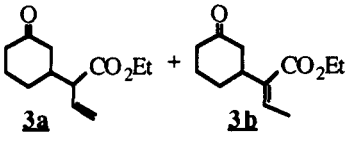
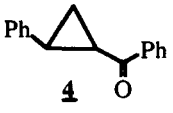
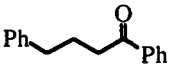
3a: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, 3H, CH_3), 1.52–2.34 (m, 9H, $4CH_2$, 1CH), 2.80 (m, 1H, CH),



5 6

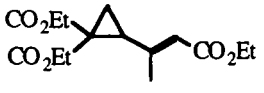
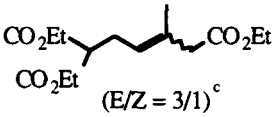
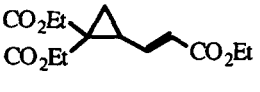
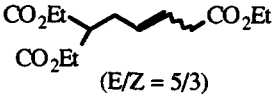
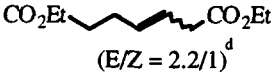
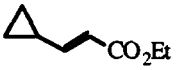
SCHEME 3

TABLE 1 Reductive Cleavage of Cyclopropyl Ketones by SmI_2

Entry	Substrates	Temp. (°C)	Time (min)	Products	Yields[a] (%)
1	 1	-78	5		91
2	 2	-78	10	 3a + 3b	85
	endo (2a)			3 : 1[b]	
	exo (2b)			2 : 1	
3	 4	-60	60		25

[a]Isolated yields.
[b]The ratio of **3a** to **3b** was determined by capillary GC, and their structures were determined by ^1H NMR (300 MHz) spectroscopy.

TABLE 2 Reductive Cleavage of Conjugated Cyclopropane Derivatives

Entry	Substrates	Temp. (°C)	Time (min)	Products	Yields[a] (%)
1		-78	1.0	 (E/Z = 3/1)[c]	89
2		-78	1.0	 (E/Z = 5/3)	91
3		-78	5.0	 (E/Z = 2.2/1)[d]	93
		-60	5.0		60
4		r.t	180		—[b]

[a]Isolated yields.
[b]Starting material was recovered (83%), and unknown products were formed.
[c]The E and Z isomer ratios were determined by ^1H NMR spectroscopy or capillary GC.
[d]Determined by integration of the allylic CH_2 protons; the E proton was upfield from that of the Z isomer.

4.09 (q, 2H, OCH_2), 5.15 (tt, 2H, $=CH_2$), 5.62–5.84 (m, 1H, =CH); ^{13}C NMR (75 MHz) δ 210.3, 172.4, 133.6, 119.1, 60.7, 56.2, 45.8, 41.1, 40.4, 28.0, 24.6, 14.16; mass (70 eV) m/z 210 (M^+, 1.6), 137 (18.4), 114 (54.3), 97 (100), 69 (55.4).

3b: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, CH_3), 1.53–1.62 (m, 3H), 1.73 (d, 3H, CH_3), 2.18–2.33 (m, 5H), 2.94 (m, 1H), 4.12 (q, 2H, OCH_3), 6.74 (q, =CH); ^{13}C NMR (75 MHz); δ 211.3, 166.8, 137.6, 134.7, 60.2, 45.5, 41.2, 37.8, 28.8, 25.7, 14.2, 13.6; mass (70 eV) m/z 210 (M^+, 55.7), 164 (93.7), 136 (86.9), 121 (63.6), 108 (74.4), 93 (59.1), 79 (75.0), 67 (81.2).

*Reductive Ring Opening of Conjugated Cyclopropanes (**5**)*

A solution of **5** (212 mg, 1.0 mmol) in THF (2 mL) and t-BuOH (1 mL) was added at −78°C to a solution of SmI_2 (2 mmol) in THF (5 mL). The resultant brown mixture was stirred for 5 minutes at −78°C, the reaction quenched at this temperature by addition of 10% aqueous K_2CO_3 solution, and then warmed to room temperature. The aqueous phase was extracted with Et_2O (5 mL × 3), and the combined extracts were dried over $MgSO_4$, concentrated in vacuo, and then chromatographed on a column of silica gel (eluent; Et_2O:n-hexane = 1:5) to give the product (197 mg, 93% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (td, 6H, 2 CH_3), 2.30 (d, 4H, 2 CH_2), 2.94, 3.05 (d, 2H, CH_2), 4.06 (qd, 4H, 2 OCH_2), 5.51 (m, 2H, —CH=CH—); IR (NaCl) 2953, 1733, 1640 cm^{-1}; mass (70 eV) m/z 214 (M^+, 6.4), 168 (26.9), 140 (66.2), 122 (40.5), 95 (37.7), 67 (100).

ACKNOWLEDGMENT

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