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Unexpected reductive double carbon–carbon bonds cleavage of bicyclic nitrocyclopropanes

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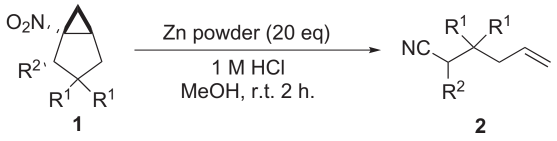
ABSTRACT

Reductive treatment of bicyclic nitrocyclopropanes with zinc powder under acidic conditions resulted in the double cleavage of carbon–carbon bonds in the cyclopropane to give vinyl nitrile in good yields. The reductive cleavage of carbon–carbon bond depended on the reaction conditions and sufficient acidic treatment gave alkenyl nitriles in good yields, while weak acidic treatment afforded oxime derivative instead.

1. Introduction

Nitrocyclopropanes are recognized as potential synthetic building blocks for aminocyclopropanes[1] or other heterocyclic compounds,[2] which are known as potentially biological active compounds. So far a variety of synthetic methods have been developed. For example, Charette and coworkers developed rhodium or copper complex-catalyzed enantioselective cyclopropanations from α-diazonitro compounds[3] or iodonium ylides derived from primary nitro compounds.[4] We have recently found a novel cyclopropanation reaction from primary nitro compounds by treatment with silver oxide, iodine, and DBU.[5] The cyclopropanation progressed in a highly diastereoselective manner and cyclopropane-fused carbo- and heterocyclic-compounds are readily prepared in a single step. Nitro group is regarded as a good precursor for amine and oxime derivatives by reductive treatment and there have been many reducing methods/reagents developed so far.[6] The products contain a nitro group at the bridgehead of the cyclopropane ring and its reduction to amine derivatives is expected to be a new construction of aminocyclopropanes.[7] We examined the reduction of the nitro group with zinc powder under acidic conditions that are usually employed for the conversion of nitrocyclopropanes into aminocyclopropanes.[6a] To our surprise, however, the expected aminocyclopropanes were not obtained under these conditions but vinyl nitriles were formed in good yields instead. Although primary nitro compounds are known to be converted into nitrile so far, this conversion is not common and only limited number of the methodologies have been known.[8] Hence, this is a new transformation to nitrile with double cleavage of carbon–carbon bonds in the cyclopropane ring. The cleavage reaction depended on the pH of the reaction conditions and oxime radical is regarded as an intermediate of the reaction. In this Letter, we report this unexpected transformation of nitrocyclopropanes that underwent double cleavage of carbon–carbon bonds in the cyclopropane ring.



Scheme 1.

2. Results and discussion

Nitrocyclopropanes **1** were prepared by reported method.[5b] Treatment of **1a** ($R^1 = CO_2Me$, $R^2 = i$Pr) with zinc powder (20 equiv) in acidic MeOH at room temperature resulted in the rapid disappearance of **1a** (Scheme 1).[9] Usual work-up after 2 h gave single compound **2a**. ^{1}H NMR for compound **2a** showed new proton peaks around 5–6 ppm, which strongly suggested that compound **2a** contained a terminal vinylic unit. ^{13}C NMR for **2a** indicated a new characteristic peak at 78.1 ppm, suggesting a nitrile carbon should be included in compound **2a**. These assumptions were also supported by FT-IR observation that showed a peak at 2243 cm^{-1}, which

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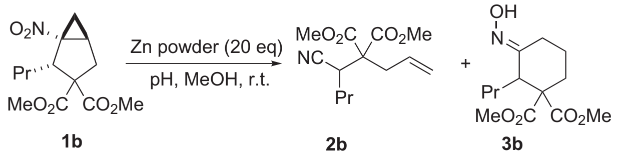
Table 1
Two carbon–carbon bonds' cleavage of nitrocyclopropane **1** under reductive conditions

Entry	R^1	R^2	Time (h)	Solvent	**2**; yield[a] (%)
1	CO_2Me	*i*Pr	2	MeOH	**2a**; 64
2	CO_2Me	Pr	2	MeOH	**2b**; 67
3	CO_2Me	Pr	12	MeOH	**2b**; 65
4	CO_2Me	Pr	2	*i*PrOH	**2b**; 62
5	CO_2Me	Et	2	MeOH	**2c**; 75
6	CO_2Me	Bu	2	MeOH	**2d**; 70
7	CO_2Me	nC_5H_{11}	2	MeOH	**2e**; 66
8	CO_2Me	nC_6H_{13}	2	MeOH	**2f**; 66
9	CO_2Me	cC_6H_{11}	2	MeOH	**2g**; 67
10	CO_2Et	Et	2	MeOH	**2h**; 69
11	CO_2Et	*i*Pr	2	MeOH	**2i**; 67
12	CO_2Et	nC_5H_{11}	2	MeOH	**2j**; 73

[a] Isolated yield.

Table 2
pH dependence of the reductive cleavage of nitrocyclopropane **1b**



Entry	pH	Time (min)	Yield[a] (%)		
			1b	**2b**	**3b**
1	4.5	5	0	45	18
2	4.8	5	0	39	22
3	5.7	5	19	18	27
4	6.1	5	66	0	19
5	6.1	15	64	0	6

[a] Isolated yield.

should be derived from a nitrile group. Note that no peaks derived from nitro groups were observed. Thus, we thought that the nitro group **1** disappeared under the reductive conditions of the reaction. Exact TOF-MS spectra indicated the molecular ion peak at 254.1389, which suggest that the atomic composition of protonated **2a** as $C_{13}H_{20}NO_4$. Based on these information we concluded that the structure of **2a** was vinyl nitrile depicted in Scheme 1. It was quite surprising that the two carbon–carbon bonds of the cyclopropane ring in **1** were cleaved in one pot. The isolated yield of **2a** was 64%.

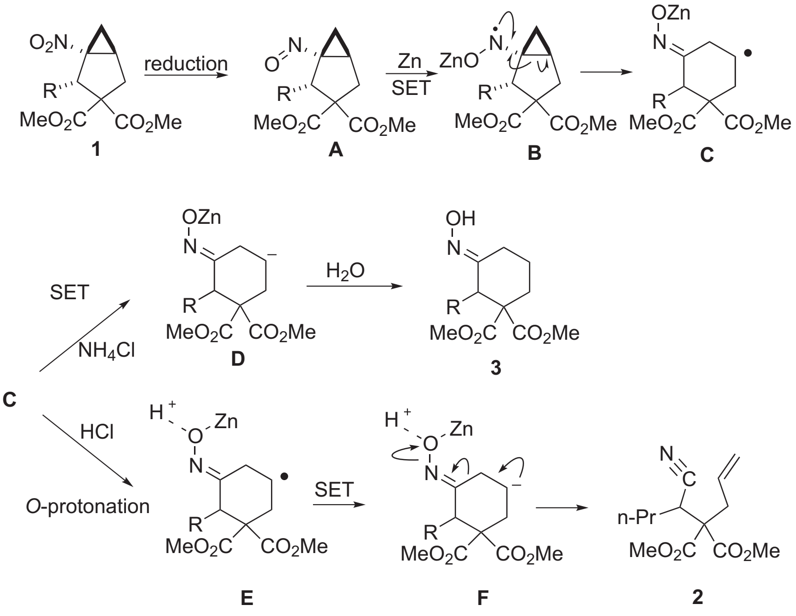
As the structure of **2a** was determined, we next examined the generality of the reduction. The results are summarized in Table 1.

For example, the reaction completed within 2 h to give compound **2b** in 67% yield (entry 2). Longer reaction time did not improve the yield of **2b** (entry 3). Use of *i*PrOH afforded **2b** in 62%, which was in a similar level of the reaction in MeOH (entry 4). Thus, the conversion for other nitrocyclopropanes **1** was performed under the conditions in MeOH for 2 h. Nitrocyclopropanes **1** were readily cleaved to give vinyl nitriles **2** in moderate to good yields (entries 5–9). The steric sizes of R^1 did not affect the efficiency of the reaction. Ethyl esters also afforded the corresponding vinyl nitriles **2h**–**2j** in good yields (entries 10–12).

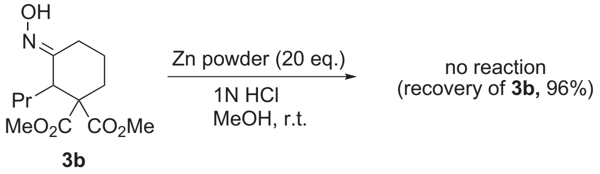
Use of NH_4Cl aq instead of aqueous HCl alternated the reaction products (Table 2). For example, treatment of **1b** with saturated NH_4Cl in the presence of zinc powder for 2 h resulted in the formation of complex mixture. Rapid disappearance of **1b** was observed so that we quenched the reaction in 5 min. Compound **2b** was isolated in 45% yield along with the other product **3b** (Table 2, entry 1). ^1H NMR for **3b** showed a new broad peak at 8.82 ppm, and ^{13}C NMR indicated a peak at 158.1 ppm, suggesting the existence of a C=N carbon. These peaks supported that **3b** contained an oxime unit. No peaks suggesting the existence of nitrile were observed.

The formation of oxime **3b** depended on the pH of the reaction conditions. The results are summarized in Table 2.

The pH of the reaction mixture was controlled by buffer solution using NH_4Cl. Actual pH values were measured by a pH meter. The reaction mixture treated under pH 4.5 or 4.8 underwent the formation of a mixture of **2b** and **3b** although the starting material **1b** was completely consumed (entries 1 and 2). As the pH value increased, the yield of **2b** decreased and starting material **1b** remained in the reaction mixture (entries 3–5). For example, the reaction performed at pH 5.7 gave **2b** in 18% yield along with



Scheme 2.



Scheme 3.

recovery of starting material **1a** in 19%, while no formation of **2b** was observed in the reaction performed at pH 6.1 (entries 3 and 4). The yields of **3b** were about 18–27% throughout these entries (entries 1–4). Prolonged reaction time never improved yield of **2b**, but the yield of **3b** decreased (entry 5).

The present double cleavage of cyclopropane was assumed to pass through the following reaction mechanism (Scheme 2).

Zinc powder under acidic conditions reduced the nitro group of **1** to give nitrosocyclopropane **A**, which may accept one electron from excess amounts of zinc powder to generate radical **B**. Intermediate **B** underwent cleavage of cyclopropane to give oxime radical **C**. When the reaction was carried out under less acidic conditions such as in aqueous NH_4Cl, the second electron transfer took place to give anion **D** that underwent immediate protonation to give oxime **3**. On the other hand, the reaction under strong acidic conditions, the oxime was protonated to generate **E** and the second electron transfer induced E1cb-type elimination from **F** to give acyclic nitrile **2**. The reaction pathways depended on the acidity of the reaction conditions; under strongly acidic conditions using aqueous HCl, the reaction progressed through **E** to **2** exclusively. Although oxime radical **C** was assumed as the key reaction intermediate, oxime **3** was no longer a reaction intermediate once it was formed. Indeed, treatment of **3b** under aqueous HCl conditions in the presence of zinc powder failed the conversion to **2b** but resulted in the recovery of **3b** in 96% (Scheme 3).

In conclusion we have found a novel conversion of bicyclic nitrocyclopropanes into vinyl nitriles in good yields. This reaction contains double carbon–carbon bonds' cleavages. During the reduction, generation of radicals that induce carbon–carbon bond cleavage is assumed and this is potentially useful to generate remote radicals from the reaction center. Further exploration on this reaction is now underway in our laboratory.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.094.

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9. *Typical experimental procedure: Preparation of dimethyl 2-allyl-2-(1-cyanobutyl)malonate (**2b**):* Zinc powder (1.4610 g, 22.3 mmol) was washed with 1 M HCl (5 mL), water (5 mL), and EtOH (2 × 10 mL) in this order and dried in vacuo. Dimethyl 1-nitro-2-propylbicyclo[3.1.0]hexane-3,3-dicarboxylate (**1b**, 306.8 mg, 1.08 mmol) was dissolved in MeOH (20 mL) and 1 M HCl (10 mL) was added. Pretreated Zn powder was added to the reaction solution at room temperature over 10 min and the resulting mixture was stirred for 2 h at room temperature. Aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture. The reaction mixture was filtered over celite and the filtrate was concentrated to about half of its volume in vacuo to remove MeOH. The resulting aqueous solution was extracted with EtOAc (3 × 30 mL). The organic phase was dried over $MgSO_4$. Crude product **2b**, obtained by filtration and concentration, was purified by flash chromatography (silica gel/hexane–EtOAc 10:1 v/v) to give **2b** in 62% yield (184.2 mg, 0.727 mmol). Colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (dq, J = 9.9, 7.4 Hz, 1H), 5.20 (d, J = 17.0 Hz, 1H), 5.16 (d, J = 10.1 Hz, 1H), 3.77 (s, 6H), 3.13 (dd, J = 11.3, 3.3 Hz, 1H), 2.82 (dd, J = 14.5, 7.4 Hz, 1H), 2.76 (dd, J = 14.5, 7.5 Hz, 1H), 1.70–1.36 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 168.9, 131.0, 120.8, 119.4, 59.0, 53.1, 53.0, 37.7, 35.2, 30.2, 21.0, 13.4; IR (neat) 2243 cm^{-1}; HRMS (ESI M+H) m/z 254.1389. Calcd for $C_{13}H_{20}NO_4$ 254.1392.