

Debromination of α -Bromoketones and *vic*-Dibromides Using a NaI/Na₂SO₃ System[†]

Seung Hwan Lee, Yu Mi Chang, and Cheol Min Yoon^{‡*}

Graduate School of Biotechnology, [‡]Department of New Material Chemistry, Korea University, Seoul 136-701, Korea

Received May 24, 2004

Key Words : Sodium iodide, Debromination, α -Bromoketone, *vic*-Dibromide

The chemical methods of dehalogenation have been important for degradation of halogenated compounds.¹ Many reagents for reduction of α -bromoketones have been developed and could be divided in three categories: (1) reducing agents, (2) nucleophilic reducing agents, and (3) Pd-catalyzed hydrogenation. Among nucleophilic reducing agents, iodide ion has been used as a mild dehalogenating agent.² Excess amount of sodium iodide in the absence of any other additives or along with other carbonyl activating additive such as sulfuric acid, chlorotrimethylsilane have been employed for the reduction of α -haloketones. Recently, stoichiometric amount of HBr as bromide source has been reported for regioselective bromination of α -haloketones in the presence of stoichiometric amount of sodium dithionite (Na₂S₂O₄) as a scavenger of bromine.³ The limitation of these reaction conditions is excess amount of reducing agent and additive, strong acidic condition or anhydrous condition required. During the study for the mild debromination condition, it occurred to us that catalytic amount of nucleophilic reducing agent could be a nice combination for the mild debromination.⁴ The debromination using a catalytic amount of nucleophilic iodide anion in the presence of sulfur salts as a reducing agent was examined and it was found that α -bromoketones and *vic*-dibromides were debrominated efficiently (Scheme 1). The advantage of this method compared to that using excess amount of iodide is that this method is that a treatment of the iodine monobromide with a large amount of sulfur reagent are not necessary during the work-up.

At first, sodium iodide, sodium sulfite and 2-bromo-3'-nitroacetophenone were selected as nucleophilic reducing agent, reducing agent of I-Br or I₂ and model substrate for

optimization of solvent system of the debromination. Debromination of 2-bromo-3'-nitroacetophenone (0.2 mmol) with 0.1 equiv. of NaI in the presence of 2 equiv. of Na₂SO₃ in acetic acid (1.5 mL) gave the 3'-nitroacetophenone in quantitative yield (Table 1 entry 1). When debrominations in the same scale were conducted in other solvent systems such as methanol, THF, aqueous THF⁵ and acetonitrile with 10 equiv. of acetic acid, similar results were obtained in yields, but the reactions were slower. The reaction in aqueous THF (entry 4) is better in yield and faster than that in THF (entry 3).

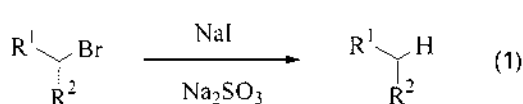
Other various iodide anion sources⁶ such as KI, TBAI, I₂ and LiI were turned out to show similar efficiency.⁷ However, debromination using various bromide sources such as NaBr, KBr, TBAB and LiBr instead of sodium iodide did not take place at all. Several other sulfur scavengers were examined (Table 2). When anhydrous Na₂S₂O₃ was used in the place of anhydrous Na₂SO₃, 2-bromo-3'-nitroacetophenone afforded the corresponding

Table 1. Debromination in various solvents^a

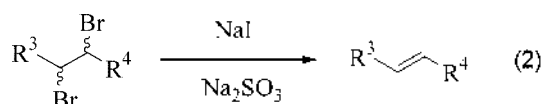
Entry	Solvents	Time	Yield ^b
1	Acetic acid	5 min	99.9%
2	MeOH	2.5 h	96.0%
3	THF	20 h	94.2%
4	THF/water (2 : 1)	20 min	98.1%
5	Acetonitrile	24 h	95.4%

^aThe reactions were conducted with 2-bromo-3'-nitroacetophenone (0.2 mmol), NaI (0.1 equiv.) and Na₂SO₃ (2 equiv.) in the presence of acetic acid (10 equiv.) in the specific solvents (1.5 mL) at room temperature.

^bIsolated yields.



R¹ = ArCO- and R² = -H or -Me;
 R¹ = BnOCO- or PhNHCO- and R² = -H;
 R¹ = Ph- and R² = -CN



R³ = Ar- and R⁴ = -COMe or -COPh or -CO₂Me or -Ph

Scheme 1

[†]Dedicated to Professor Yong Hae Kim in admiration of his contributions to organic chemistry

^{*}Corresponding Author. Fax: -82-2-3290-3433; e-mail: cmyoon@korea.ac.kr

Table 2. Debromination in the presence of various sulfur compounds^a

Entry	Sulfur compounds	Time (h)	Yield (%) ^b
1	Na ₂ SO ₃	5 min	99.9%
2	Na ₂ S ₂ O ₃	5 min	99.0%
3	Na ₂ S ₂ O ₃ ·5H ₂ O	20 min	88.4%
4	NaHSO ₃	40 min	93.9%
5	NaHS·xH ₂ O ^c	10 min	79.0%

^aThe reactions were conducted with 2-bromo-3'-nitroacetophenone (0.2 mmol), NaI (0.1 equiv.) and sulfur compounds (2 equiv.) in acetic acid (1.5 mL) at room temperature. ^bIsolated yields. ^c4 equiv. of NaHS·xH₂O was used to be complete the reaction.

ketone in quantitative yield. The same reduction in the presence of other sulfur compounds such as Na₂S₂O₃·5H₂O, NaSH·xH₂O and NaHSO₃ was also effective. When sulfur reagents alone listed in Table 2 were used, 2-bromo-3'-nitroacetophenone was remained intact except for sodium thiosulfate.⁸

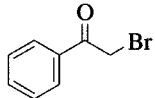
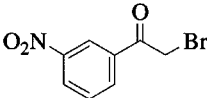
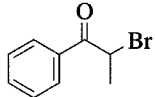
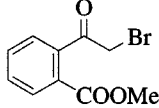
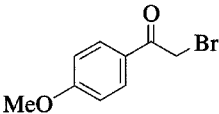
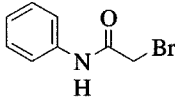
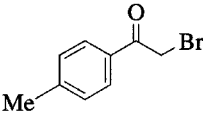
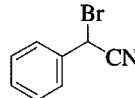
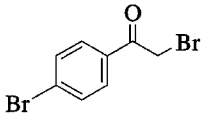
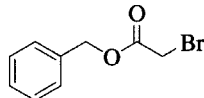
After the series of experiments, sodium iodide and sodium sulfite were the reagents of choice, due to the personal preference. The dehalogenation of various 2-bromoketones using a protocol of 0.1 equiv. of sodium iodide and 2 equiv. of sodium sulfite was tried to give the results shown in Table 3. Reduction of primary 2-bromoketone (entry 1) proceeded more readily than that of secondary bromoketone (entry 2). Debrominations of aromatic 2-bromoketones with electron donating group (entries 3, 4) and electron withdrawing group (entries 5, 6, 7) afforded the corresponding ketones in high yields. Bromo, nitro and ester substituents on phenyl ring remained intact under the reaction condition (entries 5,

6 and 7). The bromo group at *alpha* position of amide, cyanide and ester was not reduced even after 24 h stirring (entries 8-10) that open the possibility of selective debromination under our reaction condition.

The bromination of alkenes and subsequent debrominations of the resulting *vic*-dibromides offer a means for protection of the carbon-carbon double bond in synthesis and a lot of reagents have been reported.^{2f} The reaction of 3,4-dibromo-4-phenylbutan-2-one in the presence of 0.1 equiv. of sodium iodide and 2 equiv. of sodium sulfite in neat acetic acid at room temperature was not successful due to the solubility problem of substrate. Among the solvents such as methanol, THF, aqueous THF, and acetonitrile in the presence of acetic acid, acetonitrile was identified to be the best solvent in yield as shown in Table 4. Whereas dibromides with ester and ketone in acetonitrile at room temperature were debrominated to provide the corresponding alkenes in high yields (entries 1-7), the dibromide possessing phenyl (entry 8), aldehyde (entry 9) and ester (entry 10) at room temperature did not proceed under the reaction condition. When the reflux condition was applied to three substrates (entry 8-10), only the diphenyl (entry 8) gave the expected debrominated product in high yield. Debromination of relatively electron-rich dibromides involving phenyl and ester or ketone (entries 1-8) seemed to be more effective than that involving phenyl and aldehyde (entry 9) or two esters (entry 10) due to the stabilization of transition state.

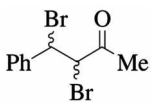
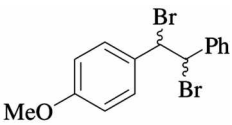
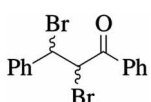
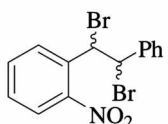
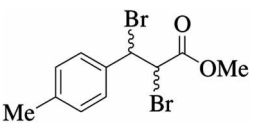
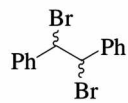
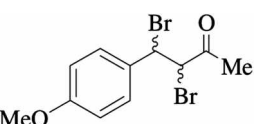
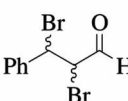
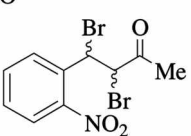
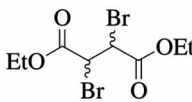
In conclusion, aromatic 2-bromoketones are effectively dehalogenated to the corresponding ketone by the catalytic amount of NaI as nucleophilic reducing agent and 2 equiv. of

Table 3. Debromination of α -bromoketone derivatives by the catalytic amount of NaI^a

Entry	Substrate	Time	Yield ^b	Entry	Substrate	Time	Yield ^b
1		0.5 h	83.6%	6		5 min	99.9%
2		3 h	91.7%	7		2 h	90.4%
3		20 min	97.2%	8		24 h	N.R.
4		30 min	95.0%	9		24 h	N.R.
5		30 min	94.2%	10		24 h	N.R.

^aThe reactions were conducted with substrate (0.2 mmol), NaI (0.1 equiv.) and Na₂SO₃ (2 equiv.) in acetic acid (1.5 mL) at room temperature. ^bIsolated yields.

Table 4. Debromination of *vic*-dibromides by the catalytic amount of NaI in acetonitrile^a

Entry	Substrate ^b	Time	Yield ^{c,d}	Entry	Substrate ^b	Time	Yield ^{c,d}
1		24 h	91.3%	6		24 h ^e	91.5% ^e
2		16 h	96.5%	7		20 h ^e	96.6% ^e
3		12 h	98.3%	8		8 h ^f (2 h) ^g	95.7% ^f (93.9%) ^g
4		3 h	95.1%	9		24 h ^b	N.R.
5		5 h	98.3%	10		24 h ^b	N.R.

^aThe reactions were conducted with dibromide (0.2 mmol), NaI (0.1 equiv.) and Na₂SO₃ (2 equiv.) in the presence of acetic acid (10 equiv.) in acetonitrile (1.5 mL) at room temperature. ^bAll dibromides were prepared by bromination of (*E*)-alkenes with bromine in CCl₄ at rt. ^cThe *E*- or *Z*-form was determined by ¹H NMR spectroscopy. ^dIsolated yields. ^eAt rt in the absence of acetic acid. ^fThe reflux condition in the absence of acetic acid. ^gAt reflux condition.

sodium sulfite as a scavenger in acetic acid at room temperature. KI, TBAI, LiI and I₂ were all found to be as effective as NaI in the debromination reaction. Our method is very useful because it is cheap and easy to use. The *vic*-dibromides as a protected form of alkene were debrominated by a protocol of NaI/sodium sulfite at rt in acetonitrile in the presence of acetic acid in high yields.

Experimental Section

General procedure for the debromination of α -bromoketones: To a solution of 2-bromoketone (0.2 mmol) in acetic acid (1.5 mL) was added sodium iodide (0.1 equiv.) and sodium sulfite (2 equiv.). The reaction was stirred at room temperature until the reaction is completed (monitored by TLC). The reaction was then concentrated and ethyl acetate (10 mL) was added. The solution was washed with saturated sodium bicarbonate (10 mL), water (10 mL \times 2), brine (10 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent under vacuum gave the reduced product, which was further purified by silica gel column chromatography with a solution of ethyl acetate and hexane (1 : 10), and characterized by ¹H NMR spectroscopy.

General procedure for the debromination of *vic*-dibromides: To a solution of *vic*-dibromide (0.2 mmol) and acetic acid (4 equiv.) in acetonitrile (1.5 mL) was added NaI (0.1 equiv.) and Na₂SO₃ (2 equiv.). The reaction was stirred at room temperature until the reaction is completed (monitored by TLC). The reaction was worked up and

purified in the same way as debromination and characterized by ¹H NMR spectroscopy.

Acknowledgements. The authors wish to acknowledge the financial support of the Korea Science and Engineering Foundation (KOSEF) made in the program year 2004.

References and Notes

- For reviews: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009.
- (a) Gemal, A. L.; Luche, J. L. *Tetrahedron Lett.* **1980**, *21*, 3195. (b) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *J. Org. Chem.* **1980**, *45*, 3531. (c) Rosenkranz, G.; Mancera, O.; Gatica, J.; Djerassi, C. *J. Am. Chem. Soc.* **1950**, *72*, 1658. (d) Olah, G. A.; Vankar, Y. D.; Fung, A. P. *Synthesis* **1979**, 59. (e) Solo, A. J.; Singh, B. *J. Org. Chem.* **1965**, *30*, 1658. (f) Butcher, T. S.; Detty, M. R. *J. Org. Chem.* **1999**, *64*, 5677. (g) Ono, A.; Fujimoto, E.; Ueno, M. *Synthesis* **1986**, 570.
- (a) Choi, H. Y.; Chi, D. Y. *Org. Lett.* **2003**, *5*, 411. (b) Choi, H. Y.; Chi, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 9202.
- Butcher, T. S.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 177.
- (a) Kim, I.-K.; Jung, O. J. *Bull. Korean Chem. Soc.* **2002**, *23*(7), 990. (b) Holder, A. A.; Marshall, S. C.; Wang, P. G.; Kwak, C.-H. *Bull. Korean Chem. Soc.* **2003**, *24*(3), 350.
- (a) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; JOHN WILEY & SONS Ltd: 1995; Vol. 7, p 4587; (b) Townsend, J. M.; Spenser, T. A. *Tetrahedron Lett.* **1971**, 137.
- The debrominations with KI, TBAI, I₂ and LiI were afforded in 98.4%, 99.6%, 99.3% and 99.0% respectively.
- Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; JOHN WILEY & SONS Ltd: 1995; Vol. 7, p 4648; Nucleophilic attack by sodium thiosulfate on alkyl halides results in the formation of alkyl thiosulfate salts.