Rapid debromination of *vic*-dibromoalkanes with zinc powder in acetic acid under microwave irradiation

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Microwave irradiation of *vic*-dibromoalkanes in acetic acid containing zinc powder for 1–2 min gave the corresponding alkenes in high yields.

Keywords: debromination, *vic*-dibromoalkanes, alkenes, zinc powder, microwave irradiation

Protection–deprotection of alkenes *via* bromination-debromination is an important process in organic synthesis, especially in the purification of steroids through their dibromides. A variety of methods have been developed in this regard. Many reagents for debromination including metals such as sodium,[1] magnesium,[2] zinc,[3] selenium,[4] copper,[5] sodium sulfide,[6] titanium(III),[7] cobalt(II),[8] tellurides,[9] samarium,[10] indium,[11] and Ni(II),[12] as well as solvents such as DMF[13] and HMPA[14] have been reported. However, most debromination reactions have several drawbacks: they use an expensive metal, require high reaction temperatures, long reaction times or exhibit low yields.

Recently, we reported the microwave-enhanced synthesis of (*Z*)-vinyl bromides from 2,3-dibromoalkanoic acids in DMF in the presence of triethylamine.[15] Here, we report a facile method for a debromination of *vic*-dibromoalkanes with zinc powder in AcOH under microwave irradiation (Scheme 1). To the best of our knowledge, efficient debromination of *vic*-dibromoalkanes under microwave irradiation has not been reported.

Various conditions were examined to optimise the yield and stereoselectivity. We tested several solvents including DMF, EtOH, MeCN and H_2O, but they afforded very low yields. The best solvent for the microwave-assisted debromination is AcOH. Note that the reaction tolerated the existence of a trace amount of water: indeed, the introduction of water up to 10% to the system did not affect the reaction. Using the conventional thermal method, debromination of *vic*-dibromoalkanes with zinc powder in AcOH at 80 °C for 0.5–2.0 h gave the corresponding alkenes in 80–95% yields. Microwave irradiation of *vic*-dibromoalkanes in AcOH containing zinc powder for 1–2 min gave the corresponding alkenes in high yields. The results are summarised in Table 1. *trans*-α,β-Unsaturated acids (**2a–d**) were produced from 2,3-dibromoalkanoic acids (**1a–d**) in excellent yields. Other kinds of *vic*-dibromoalkanes such as 2,3-dibromo-3-phenylpropanoic acid methyl ester (**1e**), 2,3-dibromo-3-phenylpropanamide (**1f**), or 1,2-dibromo-1,2-diphenylethane (**1g**) similarly gave the corresponding (*E*)-alkenes in high yields. Only (*E*)-alkenes were obtained from all the substrates (entries 1–2), whether they are *erythro* (**1a–g**) or *threo* (**1h–i**). In the case of aliphatic *vic*-dibromoalkanes (entries 3-6, **1j–m**), a longer reaction time (1.5–2.0 min) was needed. This is probably due to the fact that the cation intermediate derived from an aliphatic *vic*-dibromoalkane is less stable than from an aromatic compound. Cholesteryl acetate (**2m**) can also be obtained from 5,6-dibromocholesteryl acetate (**1m**) under the same conditions.

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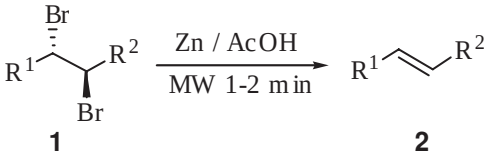
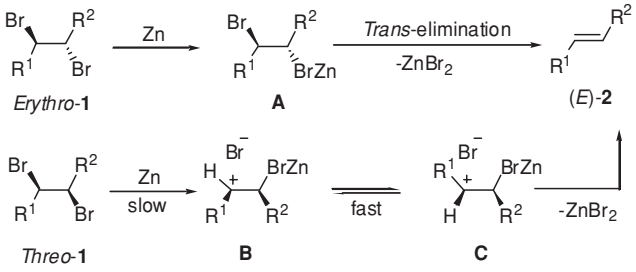


Scheme 1



Scheme 2

The proposed reaction pathways for the present stereoselective debromination are shown in Scheme 2.[3a] The reaction of the *erythro*-*vic*-dibromoalkanes (**1a–g**) is proposed to occur through *trans* elimination, in which the loss of bromide and the formation of carbon–carbon double bond take place synchronously. To account for the (*E*)-stereoselectivity in the case of *threo*-*vic*-dibromoalkane **1h** and **1i**, the carbocation (**B**) could be formed, and its C–C bond would be rotated to give the more stable carbocation conformer **C**. Finally, intermediate **C** only lead to the formation of (*E*)-alkene, the more stable isomer, presumably the process **B** →**C** is more rapid than the elimination of $ZnBr_2$.

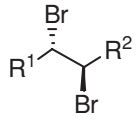
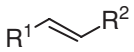
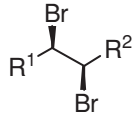
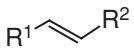
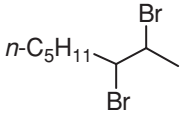
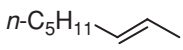
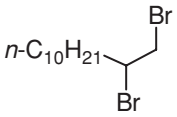
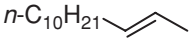
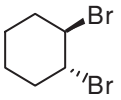
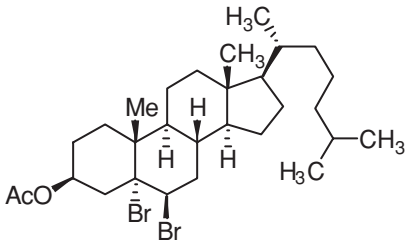
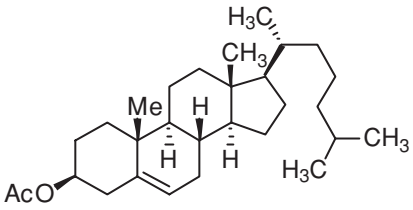
In conclusion, we have developed a rapid and convenient method for the debromination of *vic*-dibromoalkanes using a Zn/AcOH system under microwave irradiation. This was found to have significant advantages over existing procedures.

Experimental

Melting points were recorded using a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were recorded using a JASCO IR-810 IR spectrometer (between NaCl plates). ^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-EX270 FT NMR spectrometer at 270 MHz (^{1}H) and at 67.8 MHz (^{13}C) in $CDCl_3$. Chemical shifts are reported in ppm (δ) using $SiMe_4$ as an internal standard. High- and low- resolution mass spectra were determined using a JEOL JMS-FABmate or JEOL JMS-700TZ spectrometer. Column chromatography was carried out on Silica Gel 60 N (100~210 μm, Kanto Chemical Co. Ltd).

General procedure for the preparation of vic-dibromoalkanes (**1**): A solution of Br_2 (10.5 mmol) in $CHCl_3$ (30 ml) was slowly added to a solution of the alkene (10 mmol) in $CHCl_3$ (30 ml) within 30 min and stirred at ambient temperature for 3–12 h. The reaction

Table 1 Debromination of *vic*-dibromoalkanes with Zn in AcOH under microwave (MW) irridation

Entry	*vic*-Dibromoalkane	Product	MW/min	Yield/%
1				
	1a $R^1 = C_6H_5$ $R^2 = CO_2H$	**2a**	1.0	96
	1b $R^1 = 3,4\text{-}OCH_2OC_6H_3$ $R^2 = CO_2H$	**2b**	1.0	96
	1c $R^1 = 4\text{-}ClC_6H_4$ $R^2 = CO_2H$	**2c**	1.0	97
	1d $R^1 = c\text{-}C_6H_{11}$ $R^2 = CO_2H$	**2d**	1.0	98
	1e $R^1 = C_6H_5$ $R^2 = CO_2CH_3$	**2e**	1.0	98
	1f $R^1 = C_6H_5$ $R^2 = CONH_2$	**2f**	1.0	97
	1g $R^1 = C_6H_5$ $R^2 = C_6H_5$	**2g**	1.0	98
2				
	1h $R^1 = C_6H_5$ $R^2 = CO_2H$	**2a**	1.0	96
	1i $R^1 = C_6H_5$ $R^2 = C_6H_5$	**2g**	1.0	95
3			2.0	90
	1j meso/dl=95/5	**2j** E/Z = 95/5		
4			2.0	92
	1k	**2k**		
5			1.5	85
	1l	**2l**		
6			2.0	91
	1m	**2m**		

[a]Isolated yields

mixture was washed with saturated $NaHSO_3$ solution (50 ml × 2). The organic layer was separated, dried over $MgSO_4$, and concentrated. The dibromides were recrystallised (EtOAc/hexane) for **1a–i**, **1m** or distilled for **1j–l**.

1a: M.p. 197–198 °C ($CHCl_3$) (lit.[16] 196-198 °C); ^{1}H NMR ($CDCl_3$) δ 4.88 (1H, d, *J*=11.5 Hz), 5.33 (1H, d, *J*=11.5 Hz), 7.38–7.43 (5H, m).

1b: [17] M.p. 143–144 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.81 (1H, d, *J*=11.8 Hz), 5.28 (1H, d, *J*=11.8 Hz), 6.01 (2H, s), 6.77–6.90 (3H, m); EIMS *m/z* 352 ($(M+2)^+$, 19), 350 (M^+, 12), 271 (8), 226 (100); HRMS Calcd for $C_{10}H_8{}^{79}Br_2O_4$. *m/z* 349.8789. Found *m/z* 349.8788.

1c: M.p. 194–195 °C (acetone-hexane) (lit.[18] 194–195 °C); IR (nujol) 1719, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.82 (1H, d, *J*=11.5 Hz), 5.30 (1H, d, *J*=11.5 Hz), 7.20–7.40 (4H, m); EIMS *m/z* 342 ($(M+2)^+$, 5), 340 (M^+, 3), 263 (47), 137 (100); HRMS Calcd for $C_9H_7{}^{79}Br_2{}^{35}ClO_2$. *m/z* 339.8501. Found *m/z* 339.8505.

1d: [19] M.p. 158–159 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.14–1.84 (10H, m), 1.94–2.03 (1H, m), 4.36 (1H, dd, *J*=11.8 and *J*=2.3 Hz), 4.53 (1H, d, *J*=11.8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.4, 25.5, 25.9, 26.0, 32.1, 38.9, 45.1, 59.0, 173.8.

1e: M.p. 118–119 °C (EtOH) (lit.[20] 118–119 °C); ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 4.84 (1H, d, *J*=11.5 Hz), 5.34 (1H, d, *J*=11.5 Hz), 7.31–7.41 (5H, m).

1f: M.p. 216–217 °C (EtOH) (lit.[21] 217 °C); ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 5.12 (1H, d, *J*=11.5 Hz), 5.43 (1H, d, *J*=11.5 Hz), 7.35–7.41 (5H, m).

1g: M.p. 244–245 °C (toluene) (lit.[22] 243–245 °C); IR (neat) 1490, 1449, 1296, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.48 (2H, s), 7.36–7.53 (10H, m).

1h: M.p. 93–94 °C (lit.[23] 91–93 °C); ^{1}H NMR ($CDCl_3$) δ 4.75 (1H, d, *J*=10.0 Hz), 5.22 (1H, d, *J*=10.0 Hz), 7.30–7.47 (5H, m); ^{13}C NMR ($CDCl_3$) δ 50.5, 53.4, 127.8, 129.0, 129.6, 137.2, 172.4.

1i: M.p. 110 °C (lit.[24] 110 °C).

1j: [25] IR (neat) 2931, 2859, 1452, 1381, 1320, 1270, 1200, 1152, 988, 877, 846, 762, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3.0H, *J*=6.8 Hz), 1.24–1.50 (m, 5.0H), 1.56–1.66 (m, 1.0H), 1.77 (d, 0.2H,

J=6.8 Hz), 1.86 (d, 2.8H, *J*=6.8Hz), 1.90 (m, 1.0H), 2.1 (m, 1.0H), 4.08–4.14 (m, 0.93H, *meso*), 4.20–4.28 (m, 10H), 4.42–4.48(m, 0.07H, *dl*).

1k: B.p. 104–105 °C/0.3 mmHg (lit.[26] b.p. 104–105 °C/0.3 mmHg).

1l: B.p. 43–44 °C/0.5 mmHg (lit. [27] b.p. 43–44 °C/0.5 mmHg); IR (neat) 1447, 1433, 1178, 999 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–1.52 (2H, m), 1.76–1.90 (4H, m), 2.40–2.49 (2H, m), 4.51 (2H, s).

1m: M.p. 119–121 °C (EtOAc-MeOH) (lit.[28] 118–121 °C (EtOAc-MeOH)); ^1H NMR ($CDCl_3$) δ 0.70 (3H, s), 0.85–0.92 (9H, m), 0.97–1.44 (14H, m), 1.46 (3H, s), 1.48–2.02 (9H, m), 2.05 (3H, s), 2.10 (3H, s), 2.22–2.30 (1H, m), 2.54–2.72 (1H, m), 4.81–4.84 (1H, m), 5.44–5.52 (1H, m); EIMS *m/z* 588 ($(M+2)^+$, 8), 586 (M^+, 6), 507 (8), 449 (20), 427 (10), 384 (32), 368 (100), 247 (36); HRMS Calcd for $C_{29}H_{48}Br_2O_2$. *m/z* 586.2020. Found *m/z* 586.2017.

General procedure for debromination of vic-dibromoalkanes (**2**): A mixture of *vic*-dibromoalkanes (1 mmol), and Zn powder (5.0 mmol) was added to AcOH (5 ml). The mixture was kept inside a microwave oven operated at 2450 MHz (TOSHIBA, ER-V11, 200 W) and was irradiated for 1–2 min without any stirring. The reaction mixture was then removed from the oven and cooled to room temperature. Water (50 ml) and ether (50 ml) were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether (50 ml × 2). The combined organic layers were washed with water (30 ml) and brine (30 ml), and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave alkenes **2a–m**. These alkenes samples were identified by comparison of their physical and spectral data with those given in the cited references: **2a**[29]; **2b**[30]; **2c**[31]; **2d**[32]; **2e**[33]; **2f**[34]; **2g**[35]; **2j**[36]; **2k**[37]; **2l**[38]; **2m**[39]. The physical and spectroscopic data for compounds **2a** and **2l** are shown below as examples.

2a: M.p. 133–134 °C (MeOH) (lit[29] 130–131 °C); IR (nujol) 2916, 1690, 1626, 1499, 1418, 760, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.46 (1H, d, *J*=16.1 Hz), 7.39–7.44 (3H, m), 7.52–7.57 (2H, m), 7.80 (1H, d, *J*=16.1 Hz); ^{13}C NMR ($CDCl_3$) δ 117.3, 128.3, 128.9, 130.7, 133.9, 147.1, 172.7.

2l: B.p. 81–83 °C (lit.[38] b.p. 81–83 °C). IR (neat) 3032, 2982, 2840, 1651, 1441, 720 cm^{-1}; ^1H NMR (CCl4) δ 1.48–2.49 (8H, m), 5.41 (2H, m).

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