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A CONVENIENT AND EFFICIENT WORKUP OF OZONOLYSIS REACTIONS USING TRIETHYLAMINE

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Abstract: Comparison were made between triethylamine and methyl sulfide for their use as a quenching agent in the ozonolysis of a variety of alkenes. The reactions involving triethylamine often gave better yields and proceeded faster than those of involving methyl sulfide. The role of triethylamine played as base instead of reducing agent in the reaction.

Reducing agents, such as triphenylphosphine, methyl sulfide, and zinc in acetic acid have been used to attack ozonides (or α-alkoxy hydroperoxides) at a peroxide oxygen atom to give the corresponding carbonyl compounds (Pathway I, Scheme 1).[1-5] Schreiber *et al* found that α-alkoxy hydroperoxides can also be dehydrated with acetic anhydride and triethylamine to afford esters

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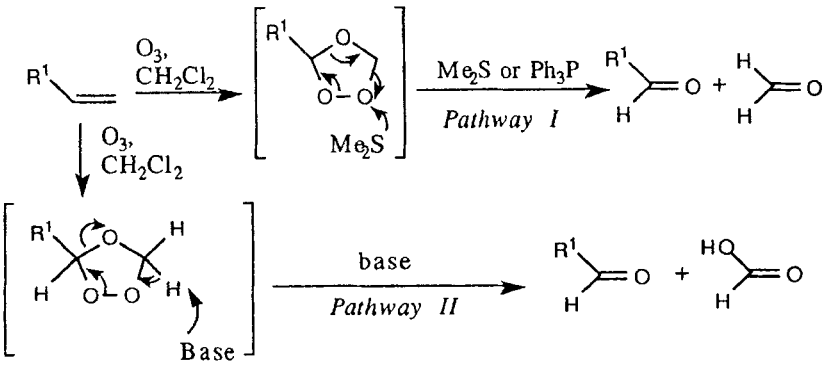
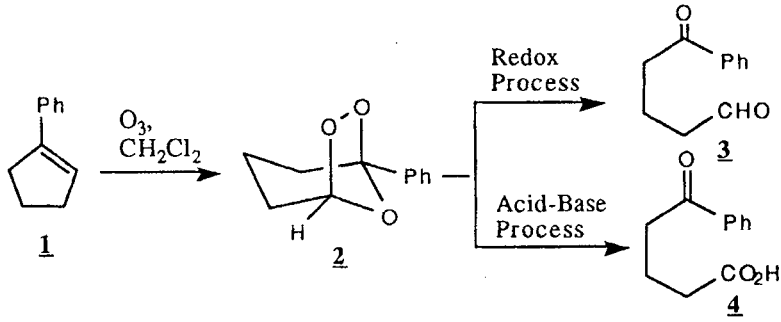


Scheme 1



Scheme 2

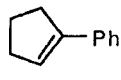
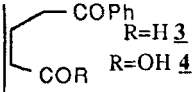
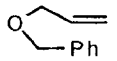
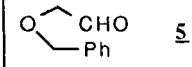
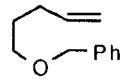
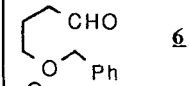
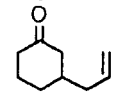
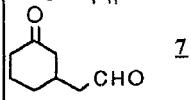
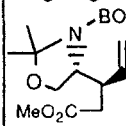
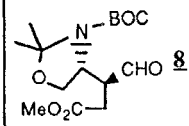
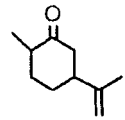
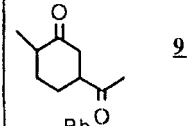
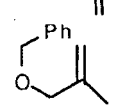
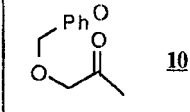
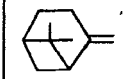
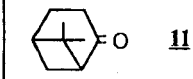
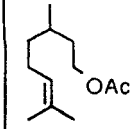
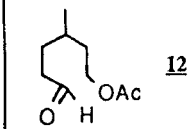
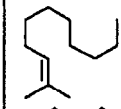
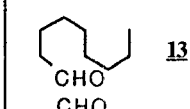
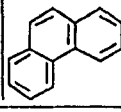
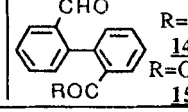
under milder conditions.[6-7] In principle, it is possible to convert the ozonides to carbonyl compounds by the base treatment (Pathway II, Scheme 1). To the best of our knowledge, little information is known about the role of the amine-type base in the ozonolysis reaction.[8-9] Amine was considered to be the reducing agent in reacting with ozonide.[10] Recently, we have reported that mono-substituted ozonides react with stable phosphorus ylides to give the Wittig-type products in high yields.[11-12] The first step of this new reaction

probably involved the deprotonation of the ozonide ring protons by the ylides. This hypothesis encourages us to clarify the mechanism and explore the synthetic applications of the reaction between the ozonides and base.

The ozonolysis of 1-phenylcyclopentene (1) gave a very high yield of the corresponding ozonide (2). Subsequently, this ozonide was treated with triethylamine or methyl sulfide to give different products in high yields (entry 1, Table 1). In comparison with the methyl sulfide treatment, the reaction time is shorter and the workup procedure is easier when triethylamine was used. The results clearly indicated that triethylamine played predominately as base, while methyl sulfide played predominately as reducing agent in the reaction (Scheme 2). It is interesting to point out that methyl sulfide also played as base to remove the ozonide ring proton, although in a minor fashion (entry 1). Apparently, the deprotonation of the ozonide ring protons is a very facile process. In order to take advantage of this chemical property in organic synthesis, the treatment of several different ozonides with triethylamine was investigated. We also compare our results with the traditional method involving methyl sulfide.

Mono-substituted ozonides from terminal alkenes were fragmented by triethylamine to give aldehydes within 4 h (entries 2–5). The chiral center at the α position in the resultant aldehyde was not epimerized during its formation (entry 5). We found that longer reaction time was required when the ozonides were treated with methyl sulfide. Some of these reactions were not complete after 40 h or longer (entries 3 and 4). The 1,1-disubstituted ozonides reacted with triethylamine to afford ketones in high yields (entries 6, 7 and 8). However, the reactions of the dihydrocarvone ozonide and β-pinene ozonide with methyl sulfide were not complete after 72 h and their yields were lower

Table 1. Reaction of Ozonides derived from Alkenes with Et_3N or Me_2S

entry	starting material	product	Et_3N Treatment time (h)	Et_3N Treatment yield	Me_2S Treatment time (h)	Me_2S Treatment yield
1		 R=H **3** R=OH **4**	12	R = H 9% & R = OH 73%	48	R = H 83% & R = OH 11%
2		 **5**	4	83%	20	81%
3		 **6**	4	80%	40	54% & 38% ozonide **16**
4		 **7**	3	88%	72	54% & 20% ozonide **17**
5		 **8**	3	78%	24	78%
6		 **9**	43	93%	72	51% & 5% ozonide **18**
7		 **10**	72	64%	72	56%
8		 **11**	8	74%	72	23% & 24% ozonide **19**
9		 **12**	—	90%[a]	—	90%[a]
10		 **13**	—	93%[a]	—	93%[a]
11		 R=H **14** R=OH **15**	48	R = H 30% & R = OH 42%	72	R = H 62% & R = OH 14%

[a] The products were formed after ozonolysis in CH_2Cl_2 at -78 °C without any reagents.

than those obtained from triethylamine treatment (entries 6 and 8). In general, for mono-substituted and 1,1-disubstituted alkenes, the use of triethylamine to workup the ozonolysis reaction afforded a better yield of carbonyl compounds in a much shorter period than the use of methyl sulfide.

Ozonolytic cleavage of tri-substituted alkenes was expected to give an acid by use of triethylamine and an aldehyde by use of methyl sulfide. However, aldehydes were obtained in high yields under both reaction conditions. Indeed, the ozonolysis of trisubstituted alkenes in dichloromethane gave aldehydes, instead of ozonides. Therefore, no reagent was needed to workup this type ozonolysis (entries 9 and 10).

In contrast to the results mentioned above, the triethylamine treatment gave almost equal amount of a dialdehyde (**14**) and an acid–aldehyde (**15**), whereas the methyl sulfide treatment afforded a dialdehyde (14) as the major product in 62% yield in the ozonolysis of phenanthrene (entry 11). Phenanthrene gave a mixture of polymeric ozonides and dialdehyde after ozonolysis and no normal ozonide can be isolated. Therefore, the rationale of their product distributions is different from the previous cases.

The standard procedure for the sequential ozonolysis of alkenes and triethylamine or methyl sulfide treatment is as follows. Ozone was introduced into a flask containing an alkene in dichloromethane at –78 ℃ until the solution turned blue. The excess ozone was excluded by nitrogen stream.[13] Two equivalents of triethylamine or ten equivalents of methyl sulfide were added to the solution, which was warmed up to room temperature. The reaction time and chemical yields were shown in Table 1. The workup procedure is extremely simple. The extraction tecnique is enough to remove the byproducts and get spectroscopically pure product.[14]

Convenient workup, low cost, mild reaction conditions, fast reaction rate, and high chemical yield make our method practical and attractive for most of ozonolysis reaction. In order to avoid the stench of the methyl sulfide treatment, the tedious separation of the triphenylphosphine treatment and the acidic condition of the zinc in acetic acid treatment, the triethylamine treatment is an excellent choice to workup the ozonolysis reaction.

ACKNOWLEDGEMENT

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14. The spectra data were taken with the following instruments. Melting points were determined using a Yanaco micro melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 Spectrometer, and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin Elmer 882 spectrophotomer and only noteworthy absorptions were listed. Mass spectra were measured on a VG 70-250S mass spectrometer by electronic impact at 70 eV (unless otherwise indicated).

Compound 2 : colorless oil; IR (neat) (ν, cm^{-1}): 3090, 3063, 3037, 2963, 2928, 1477, 1351, 1331, 1254, 1130, 1103, 1068, 1042, 937, 907; ^{1}H NMR ($CDCl_3$) δ 1.71–2.41 (m, 6H), 5.93 (s, 1H), 7.31–7.56 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.9, 28.9, 33.0, 103.5, 107.8, 125.6, 128.2, 129.2, 137.8; MS (50 eV) (m/z) : 192 (M^+, 1), 176 (1), 160 (18), 148 (8), 132 (2), 122 (19), 105 (100), 87 (15), 77 (51), 71 (67).

Compound 3 : pale yellow liquid; IR (neat) (ν, cm^{-1}): 3059, 2942, 2897, 2829, 2729, 1719 (HC=O), 1675 (PhC=O), 1596, 1442, 1365, 1226, 1177, 999, 966; ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 2H), 2.57 (td, J = 0.9 and 7.1 Hz, 2H), 3.03 (t, J = 7.0 Hz, 2H), 7.39–7.97 (m, 5H), 9.78 (s, 1H, CHO) ; ^{13}C NMR ($CDCl_3$) δ 16.3, 37.1, 42.8, 127.8, 128.4, 132.9, 136.5, 199.1 (PhC=O), 201.8 (HC=O); MS (m/z) : 176 (M^+,3), 158 (8), 148 (18), 120 (20), 105 (100), 91 (3), 77 (45); HRMS (m/z): 176.0842 (M^+, $C_{11}H_{12}O_2$, calcd 176.0837).

Compound 4 : white solid, m.p. = 123–125 ℃; IR (CH_2Cl_2) (ν, cm^{-1}): 2400–3500 (br, -OH), 1706 (C=O), 1686 (PhC=O), 1256, 1244; ^{1}H NMR

($CDCl_3$) δ 2.09 (m, 2H), 2.51 (t, J = 7.0 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 7.26–7.98 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.0, 33.0, 37.3, 128.0, 128.6, 133.1, 136.7, 178.8 (COOH), 199.4 (PhC=O); MS (m/z) : 192, (M^+, 25), 156 (56), 139 (40), 129 (17), 114 (35), 105 (100), 77 (39), 72 (40); HRMS (m/z): 192.0782 (M^+, $C_{11}H_{12}O_3$, calcd 192.0786).

COMPOUND 5 : colorless oil; IR (neat) (ν, cm^{-1}): 3451, 3067, 3032, 2913, 2866, 2825, 2247, 1732 (C=O), 1449, 1386, 1246, 1204, 1107, 1025, 891; ^1H NMR ($CDCl_3$) δ 4.08 (s, 2H), 4.61 (s, 2H), 7.29–7.37 (m, 5H), 9.69 (t, J=0.6 Hz, 1H); MS (m/z): 150 (M^+, 2), 129 (1), 121 (4), 107 (47), 91 (100), 77 (10), 65 (20); HRMS (m/z): 150.0668 (M^+, $C_9H_{10}O_2$, calcd 150.0681).

COMPOUND 6 : colorless oil; IR (neat) (ν, cm^{-1}): 3488, 3239, 3205, 3078, 3053, 2991, 2944, 1707 (C=O); ^1H NMR ($CDCl_3$) δ 1.94 (m, 2H), 2.54 (td, J = 1.6 and 7.1 Hz, 2H); 3.05 (t, J = 6.1 Hz, 2H); 4.48 (s, 2H), 9.77 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 40.9, 69.1, 72.9, 127.6, 128.4, 138.2, 202.3; MS (m/z) : 178 (M^+, 4), 150 (5), 134 (2), 123 (2), 107 (33), 91 (100), 77 (15), 71 (10), 65 (15); HRMS (m/z): 178.0986 (M^+, $C_{11}H_{14}O_2$, calcd 178.0994).

COMPOUND 7 : colorless oil; IR (neat) (ν, cm^{-1}): 2939, 1704 (C=O), 1224, 724; ^1H NMR ($CDCl_3$) δ 1.23–2.56 (m, 11H), 9.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 31.0, 33.2, 34.9, 39.4, 41.1, 47.5, 49.9, 200.6 (HC=O), 210.2 (C=O); MS (m/z) : 140(M^+, 33), 120 (94), 105 (26), 97 (100), 91 (85), 84 (72), 77 (25), 69 (82), 65 (26); HRMS (m/z): 140.0810 (M^+, $C_8H_{12}O_2$, calcd 140.0837).

COMPOUND 8 : Pale yellow liquid; ^1H NMR ($CDCl_3$) δ 1.40–1.80 (m, 15H), 2.30–3.00 (m, 2H), 3.00–3.50 (m, 1H), 3.70 (s, 3H), 3.80–4.36 (m,

3H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 23.8, 26.2, 26.8, 28.1, 29.3, 29.7, 50.6, 50.9, 51.8, 56.1, 65.0, 65.5, 66.0, 80.8, 93.9, 172.0, 200.1.

COMPOUND 9 : colorless oil; IR (neat) (ν, cm^{-1}): 2972, 2936, 2869, 1699 (C=O), 1356, 1239, 1164; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 6.5 Hz, 3H), 1.15–2.92 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 14.2, 27.8, 28.2, 34.5, 42.7, 44.6, 52.1, 208.2 (C=O), 211.4 (C=O); MS (m/z) : 154 (M^+, 23), 139 (2), 121 (2), 111 (100), 97 (12), 83 (20), 71 (11).

COMPOUND 10 : colorless; IR (neat) (ν, cm^{-1}): 2924, 2866, 2250, 1718 (C=O), 1418, 1355, 1262, 1108, 1023; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 4.05 (s, 2H), 4.58 (s, 2H), 7.31–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.2, 73.1, 75.1, 127.7, 127.8, 128.3, 137.0, 206.5; MS (m/z) : 165 (M^++1, 1), 163 (M^+-1, 1), 148 (2), 135 (1), 121 (1), 107 (60), 105 (11), 91 (100), 77 (10), 65 (20).

COMPOUND 11 : colorless oil; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.23 (s, 3H), 1.61 (d, J = 13.8 Hz, 1H), 1.88–2.69 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 21.26, 21.97, 25.12, 25.76, 32.64, 40.28, 41.05, 57.84, 214.66

COMPOUND 12 : colorless oil; IR (neat) (ν, cm^{-1}): 2963, 2931, 1720, 1365, 1231, 1054 ; ^1H NMR ($CDCl_3$) δ 0.9 (d, J = 8.5 Hz, 3H), 1.21–1.71 (m, 4H), 2.05 (d, J = 0.6 Hz, 3H), 2.47 (td, J = 1.5 and 6.8 Hz, 2H), 4.11 (td, J = 2.2 and 6.6 Hz, 2H), 9.78 (t, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.0, 20.9, 28.6, 29.4, 35.1, 41.4, 62.5, 171.1 (C=O), 202.3 (C=O).

COMPOUND 13 : Its spectrum is idetical to that of 1-nonanal.

COMPOUND 14 : pale yellow solid, m. p.= 51–53 °C; ^1H NMR ($CDCl_3$) δ 7.36 (dd, J = 1.1 and 6.1 Hz, 2H), 7.63 (m, 4H), 8.06 (m, 2H), 9.83 (d, J = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 128.5, 128.7, 131.6, 133.4, 134.5, 141.2, 191.0; MS (m/z) : 210 (M^+, 20), 181 (100), 152 (61), 135 (10), 120

(16), 105 (36), 91 (8), 77 (16); HRMS (m/z): 210.0688 (M^+, $C_{14}H_{10}O_2$, calcd 210.0681).

COMPOUND 15 : yellow solid, m. p. = 114–116 ℃; IR (CH_2Cl_2) (ν, cm^{-1}): 2500–3600 (br, -OH), 1690 (C=O), 1597, 1398, 1285, 726; ^1H NMR ($CDCl_3$) δ 7.16–8.11 (m, 8H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 128.3, 127.6, 128.1, 130.0, 130.2, 130.8, 131.8, 133.0, 133.6, 139.5, 171.4 (COOH), 191.6 (CHO); MS (m/z) : 181 (M^+-45, 3), 149 (3), 119 (8), 115 (8), 84 (100), 72 (1); HRMS (m/z): 181.0649 (M^+-45, $C_{13}H_9O$, calcd 181.0653).

COMPOUND 16 : colorless oil; ^1H NMR ($CDCl_3$) δ 1.80 (m, 4H), 3.51 (t, J = 5.8 Hz, 2H), 4.51 (s, 2H), 5.04 (s, 1H), 5.18 (s, 2H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.0, 28.1, 69.5, 72.8, 94.0, 103.5, 127.5, 128.3, 138.3.

COMPOUND 17 : colorless oil; IR (neat) (ν, cm^{-1}): 2941, 1701, 1448, 1431, 1400, 1381, 1348, 1313, 1286, 1229, 1203, 1183, 1101, 1059; ^1H NMR ($CDCl_3$) δ 1.40–2.30 (m, 11H), 5.04 (s, 1H), 5.18 (s, 1H), 5.18 (s, 1H), 5.19 (t, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 30.9, 31.0, 34.5, 37.3, 40.7, 47.5, 47.6, 93.6, 101.9, 201.0; MS (m/z) : 156 (M^+-30), 139, 112, 97 (100), 95, 84, 69, 58, 55; HRMS (m/z): 156.0758 (M^+-30, $C_{13}H_9O$, calcd 156.0786).

COMPOUND 18 : colorless oil; IR (neat) (ν, cm^{-1}): 2968, 2935, 1705 (C=O), 1374, 1212, 1132, 1102, 1058, 964, 904; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 6.4 Hz, 3H), 1.36–2.55 (m, 10H), 5.11 (d, J = 15.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.0, 20.4, 26.1, 26.4, 34.0, 42.4, 42.6, 44.6, 46.3, 94.0, 94.1, 109.8, 211.4 (C=O).

COMPOUND 19 : colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.23 (s, 3H), 1.58 (d, J = 10.5 Hz, 1H), 1.64–2.38 (m, 7H), 4.99 (s, 1H), 5.07 (s, 1H); . ^{13}C NMR ($CDCl_3$) δ 22.40, 22.77, 26.16, 26.40, 27.73, 40.02, 49.10, 92.86.

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