A Convenient Procedure for Oxidation of Phosphorus Ylides to Their Corresponding Oxo-derivatives Using *m*-CPBA under Mild Conditions

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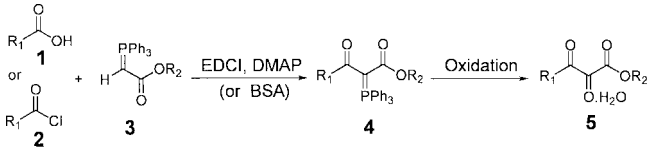
Received August 25, 2000

Vicinal tricarbony systems[1] have attracted considerable renewed interest in the last several years since these systems have been found to occur in the potent immunosuppressant FK-506,[2] rapamycin and 29-demethoxyrapamycin,[3] and other biologically important complicated compounds.[4] This structural unit has been recognized as one of the most electrophilic structural units together with trifluoromethylketone,[5a,b] α-diketone,[5c,d] α-keto ester and amide,[5e,f] and has been believed engaged in enzyme-inhibition *via* formation of a hemiketal-type intermediate upon reaction with hydrolytic enzymes such as α-chymotrypsin, porcine pancreatic elastase, human neutrophil elastase.[6]

While a variety of synthetic methods[7] have been reported so far, most of these relied on the tactics in which vicinal tricarbonyl systems were prepared *via* oxidation of the active methylene or its derivatives of β-keto (or β-hydroxy) ester (or amide) with appropriate oxidizing agents. Unlike the above-mentioned methods, Wasserman's approach[8] utilized phosphorane ylides to introduce the vicinal tricarbonyl precursors into the target molecules in a convergent manner, therefore, has appeared one of the best synthetic methods for this highly electrophilic fragment (Scheme 1). This approach has been successfully applied to the synthesis of structurally complicated natural products *e.g.* "tricarbonyl" region of FK-506,[9] and depsipeptide elastase inhibitors, YM-47141 and YM-47142.[10]

One of the key steps for this process is the oxidative cleavage of a carbon-phosphorus double bond, and several oxidants such as $NaIO_4$,[11a] triphenyl phosphite-ozone,[11b] *N*-sulfonyloxaziridines,[11c] singlet oxygen,[9] ozone,[11d] oxone,[11e] and most recently dimethyldioxirane[11f] have been reported. These oxidants, however, may have some limitations, *e.g.*, vigorous reaction conditions, instability of reagent itself above -35 °C, very expensive price, use of photochemical reaction kit, destructive oxidation of double bond, heterogeneous reaction conditions and prolonged reaction time, and/or poor selectivity and *etc*. Among the oxidants reported, dimethyldioxirane[11f] seems to be the reagent of choice, however, necessitating careful controls (*e.g.*, amount of oxidant, reaction temperature and time) to get high selectivity and unavailability from commercial sources may preclude this reagent from being widely used. Therefore, there is a need for a mild and readily available oxidant for this oxidative conversion.



Scheme 1

During the study of developing a new synthetic methodology[12] for vicinal tricarbonyls based on phosphorus ylide chemistry, we found that *m*-chloroperoxybenzoic acid (*m*-CPBA), the widely used and commercially available oxidizing agent, readily cleave the carbon-phosphorous double bond. Thus, we have done a systematic study for this new oxidative protocol, and herein we wish to report our preliminary results.

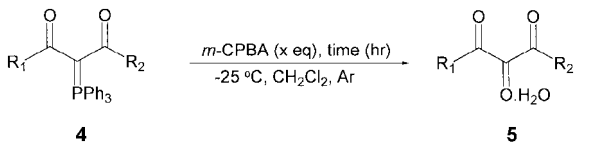
Results and Discussion

The starting phosphorus keto ylides **4** were synthesized from the corresponding carboxylic acids **1** (or their acid chlorides **2**) and the appropriate (triphenylphosphoranylidene) acetates **3** following the reported procedures[8b] in good yields (Scheme 1).

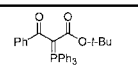
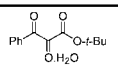
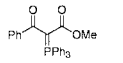
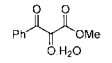
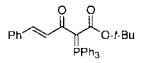
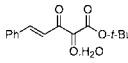
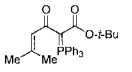
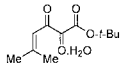
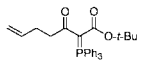
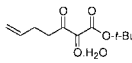
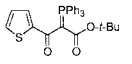
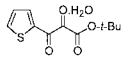
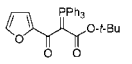
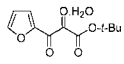
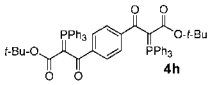
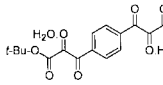
m-CPBA has been known a versatile oxidizing agent capable of reacting with many functional groups.[13a] We were particularly concerned about epoxidations of alkenes,[13b,c] and Baeyer-Villiger type oxidations of ketones to esters,[13d] since many biologically important natural products incorporating tricarbonyls[2,3] are also carrying these functional groups. Therefore, it was sought to carry out the new oxidative cleavage of a carbon-phosphorus double bond under reasonably mild conditions as possible to suppress the above-mentioned side reactions. The representative results of our new oxidative protocol using *m*-CPBA are summarized in Table 1.

In optimization of reaction conditions, phosphorus keto ylide **4a** was tested as a starting material: When **4a** in CH_2Cl_2 was treated with 2 equivalent of *m*-CPBA at various reaction temperatures (-78 °C, -40 °C, -25 °C), *ca.* 30%, 60%, 90% of oxidative conversions were observed respectively in 2h, and no further reaction progresses were made even after being stirred for 5h. Theoretically, two equivalent of *m*-CPBA was expected to be enough for the complete oxidation of **4a** to tricarbonyl **5a** and triphenylphosphine oxide **6**.[11b,14] However, a slight stoichiometric excess of *m*-CPBA (*ca.* 2.3 eq) was required to force the reaction to completion in 1.5 h at -25 °C. Oxidation of methyl ester analogue **4b** required longer reaction time (2.0 h) compared to **4a** apparently due to the less nucleophilic nature of the ylide carbon. Under these optimized reaction conditions (-25 °C, *ca.* 2.3 eq of *m*-CPBA, 1.5 h, CH_2Cl_2), the phosphorus keto ylides **4c**, **4d** with a conjugated double bond, and **4e** with an iso-

Table 1. The Selective Oxidation of Phosphorus Ylides to their Corresponding Tricarbonyls



4 **5**

Entry	Phosphorus Ylides		eq	Time (hr)	Products (Yield, %)
1		**4a**	2.3	1.5	 **5a** (96)
2		**4b**	2.3	2.0	 **5b** (90)
3		**4c**	2.3	1.5	 **5c** (91)
4		**4d**	2.3	1.5	 **5d** (96)
5		**4e**	2.3	2.0	 **5e** (85)
6		**4f**	2.3	1.5	 **5f** (92)
7		**4g**	2.3	1.5	 **5g** (87)
8		**4h**	4.8	2.0	 **5h** (76)

lated double bond were transformed cleanly into tricarbonyls without forming observable amounts of epoxidized or Baeyer-Villiger type oxidized byproducts.

The synthesis of tricarbonyls with heterocyclic substituents draws special attention since numerous compounds containing heterocyclic moieties have exhibited biologically interesting properties.[15] In view of sulfur atom and ring itself of thiophene derivatives being oxidized with appropriate electrophilic oxidizing agents,[16] it is noteworthy that thiophene-substituted keto ylide **4f** was oxidized selectively without forming detectable amounts of thiophene ring- and/or *S*-oxidized byproducts. This result signifies that the ylide carbon of **4f** is far more nucleophilic than the sulfur atom and the ring carbon of thiophene toward the electrophilic oxygen of *m*-CPBA. Furan-derived keto ylide **4g** also exhibited the similar result under the same conditions.

A number of natural and synthetic substances having cytotoxicity and antitumor antibiotic activity, which can be attributed to interstrand DNA cross-linking ability, have been reported in recent years.[17] In this respect, the synthesis of bis-vicinal tricarbonyl **5h**, reported as an effective interstrand DNA cross-linking agent.[18] is of special interest. Thus bis-phosphorus ylide **4h** tethered by aromatic ring was smoothly oxidized in 76% yield under the similar reaction conditions.

In conclusion, *m*-CPBA was found to be an efficient and practical oxidizing agent for the selective oxidation of carbon-phosphorous double bonds in the presence of a number of oxidizable functional groups under mild conditions. The reaction conditions were mild and the yields were good to excellent. We are continuing to explore the scope of this new oxidation reaction and investigating the possibility of applying this new oxidation protocol to the phosphorus keto ylides with nitrogen heterocycles and peptides.

Experimental Section

All reactions were carried out in oven-dried glassware under an argon atmosphere. Melting points were taken on a Electrothermal melting-point apparatus and are not corrected. IR-spectra were recorded on a JASCO FT-IR/410 using KBr. ^{1}H NMR (400 MHz) spectra were obtained in $CDCl_3$ on JEOL-EX 400 spectrometer using TMS as the internal standard. Flash column chromatography was carried out on silica gel (Merck. 230-400 mesh) and solvents are reported as V/V percent mixtures. CH_2Cl_2 were distilled from calcium hydride. (Triphenylphosphoranylidene)acetates (*t*-butyl: **3a**. methyl: **3b**) were prepared from the corresponding bromo- (or chloro-) acetates according to the literature procedures.[19] 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP). *N,O*-bis(trimethylsilyl)acetamide (BSA) were purchased from *Aldrich Chemical Co.*. and were used without purification. *m*-CPBA (77%) was newly purchased from *Aldrich Chemical Co.* All other commercial reagents were purchased from commercial sources and were used as received unless otherwise stated. The starting phosphorus keto ylides **4**, and oxidized tricarbonyls **5** are known compounds, and their physical and spectral (IR and ^{1}H NMR) data were identical with those of reported values.[8b,11e,f,17]

Typical procedure for the synthesis of phosphorus keto ylide (4d) using BSA

3,3-Dimethylacrylic acid (810.6 mg, 8.1 mmol) was treated with oxalyl chloride (780 mL, 1.1 eq) and DMF (catalytic) in CH_2Cl_2 (10 mL) at 5 °C for 2 h under Ar. The solvent was evaporated *in vacuo* to provide the crude 3,3-dimethylacryloyl chloride which was used without purification. BSA (2.4 mL, 1.2 eq) was added to *t*-butyl (triphenylphosphoranylidene)acetate (**3a**, 3.05 g. 1.0 eq) in CH_2Cl_2 (5 mL) at 0 °C and the reaction mixture was stirred for 0.5 h. To this solution was transferred a solution of crude 3,3-dimethylacryloyl chloride in CH_2Cl_2 (5 mL) *via* cannula and the resulting mixture was stirred at 0 °C for 0.5 h, then overnight at rt under Ar. The reaction was quenched by addition of saturated brine. and separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). and the combined organic layers were washed with brine. dried over $MgSO_4$. filtered, and evaporated. The yellow residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc. 3/1) to afford **4d** as an off-white solid. Yield 70%; mp 157-158 °C; R_f 0.49 (hexanes/EtOAc. 1/1): IR (KBr) 3061, 2998. 2971, 1664 (br), 1530, 1483. 1437. 1387. 1360. 1307, 1241, 1172, 1108. 1083. 746. 693 cm^{-1}; ^{1}H NMR δ 1.08 (s, 9H). 1.86 (s. 3H). 1.90 (s. 3H), 6.92 (s. 1H), 7.44-7.49 (m, 9H). 7.71 (m. 6H).

4a: Yield 75%; an off-white solid; mp 188-189 °C; R_f 0.45 (hexanes/EtOAc, 1/1); IR (KBr) 3079, 3051, 3005, 2977, 1667 (br), 1524, 1439, 1344, 1274, 1173, 1106, 1080, 883, 751, 725, 690 cm^{-1}; ^1H NMR δ 0.96 (s, 9H), 7.33 (m, 3H), 7.46-7.53 (m, 9H), 7.67-7.68 (m, 2H), 7.76-7.81 (m, 6H).

4b: Yield 92%; an off-white solid; mp 51-52 °C; R_f 0.30 (hexanes/EtOAc, 1/1); IR (KBr) 3056, 2942, 1671 (br), 1586, 1542, 1483, 1437, 1330, 1293, 1183, 1105, 1080, 749, 722, 692 cm^{-1}; ^1H NMR δ 3.14 (s, 3H), 7.33-7.35 (m, 3H), 7.48-7.54 (m, 9H), 7.67-7.69 (m, 2H), 7.73-7.78 (m, 6H).

4c: Yield 90%; a pale-yellow solid; mp 174-175 °C; R_f 0.52 (hexanes/EtOAc, 1/1); IR (KBr) 3078, 3059, 2976, 1648 (br), 1636, 1547, 1483, 1438, 1345, 1209, 1168, 1104, 1085, 987, 770, 755, 700 cm^{-1}; ^1H NMR δ 1.10 (s, 9H), 7.23-7.32 (m, 3H), 7.40-7.52 (m, 10H), 7.56-7.58 (m, 2H), 7.70-7.75 (m, 6H), 8.19 (d, 1H, J = 16.1 Hz).

4e: Yield 75%; an off-white solid; mp 159.5-160.5 °C; R_f 0.50 (hexanes/EtOAc, 1/1); IR (KBr) 3061, 2973, 2931, 1656 (br), 1544, 1485, 1438, 1314, 1248, 1169, 1109, 1086, 998, 930, 910, 850, 750, 690 cm^{-1}; ^1H NMR δ 1.07 (s, 9H), 2.35 (q, 2H, J = 7.1 Hz), 2.97 (t, 2H, J = 7.6 Hz), 4.90 (brd, 1H, J = 10.0 Hz), 5.01 (brd, 1H, J = 15.6 Hz), 5.82-5.92 (m, 1H), 7.41-7.51 (m, 9H), 7.65-7.70 (m, 6H).

Typical procedure for the synthesis of phosphorus keto ylide (4h) using EDCI and DMAP

Terephthalic acid (497.0 mg, 3.0 mmol) and *t*-butyl (triphenylphosphoranylidene)acetate (**3a**, 2.50 g, 2.0 eq) in CH_2Cl_2 (15 mL) were treated with EDCI (1.20 g, 2.1 eq) in the presence of DMAP (catalytic) at 0 °C for 0.5 h under Ar. The reaction was allowed to reach ambient temperature and stirring was continued overnight under Ar. The reaction mixture was quenched with brine, separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to provide yellow oil, which was purified by column chloromatography (SiO_2, hexanes/EtOAc, 1/4) to afford **4h** as a pale-yellow solid. Yield 52%; mp 226.5-227.5 °C; R_f 0.23 (hexanes/EtOAc, 1/4); IR (KBr) 3056, 2973, 1666 (br), 1540 (br), 1483, 1438, 1389, 1363, 1315 (br), 1173, 1105, 1069, 896, 850, 691 cm^{-1}; ^1H NMR δ 0.98 (s, 18H), 7.45-7.51 (m, 18H), 7.70-7.80 (m, 16H).

4f: Yield 80%; a pale-yellow solid; mp 166-167 °C; R_f 0.55 (hexanes/EtOAc, 1/1); IR (KBr) 3078, 3059, 2977, 1669, 1526, 1506, 1438, 1421, 1336, 1265, 1170, 1106, 1079, 849, 688 cm^{-1}; ^1H NMR δ 1.03 (s, 9H), 7.03 (brt, 1H, J = 4.0 Hz), 7.37 (brd, 1H, J = 4.8 Hz), 7.45-7.51 (m, 9H), 7.74-7.79 (m, 6H), 7.82 (brd, 1H, J = 2.4 Hz).

4g: Yield 83%; a pale-brown solid; mp 146.5-147.5 °C; R_f 0.40 (hexanes/EtOAc, 2/1); IR (KBr) 3080, 3059, 2975, 1671 (br), 1511, 1474, 1438, 1389, 13 42, 1274, 1166, 1106, 1081, 868, 771, 741, 688 cm^{-1}; ^1H NMR δ 1.06 (s, 9H), 6.42 (brs, 1H), 7.13 (brs, 1H), 7.43-7.52 (m, 10H), 7.74-7.79 (m, 6H).

Typical procedure for the selective oxidation of phosphorus keto ylide (4a) using *m*-CPBA

To a precooled (*ca.* -25 °C), stirred solution of keto ylide **4a** (80.4 mg, 0.17 mmol) in CH_2Cl_2 (2.5 mL) was added *m*-CPBA (86.2 mg, 2.3 eq) in one portion and the resulting mixture was stirred at -25 °C for 1.5 h under Ar. The reaction was quenched by addition of saturated $NaHCO_3$ (5 mL), diluted with CH_2Cl_2 (5 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 2), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, then evaporated. The yellow residue was purified by flash column chromatography (SiO_2, hexanes/EtOAc, 3.5/1) to afford pure product **5a**. R_f 0.50 (hexanes/EtOAc, 2/1); IR (KBr) 3426 (br), 3075, 2980, 1742, 1691, 1634, 1600, 1451, 1372, 1254, 1128, 1014, 829, 705, 682 cm^{-1}; ^1H NMR δ 1.31 (s, 9H), 5.27 (brs, 2H), 7.47 (t, 2H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.8 Hz), 8.07 (brd, 2H, J = 7.6 Hz).

5b: R_f 0.32 (hexanes/EtOAc, 2/1); IR (KBr) 3468 (br), 3425 (br), 3065, 2959, 1757, 1743, 1696, 1598, 1450, 1326, 1237, 1132, 1106, 1009, 956, 814, 801, 714, 682 cm^{-1}; ^1H NMR δ 3.75 (s, 3H), 5.31 (brs, 2H), 7.48 (t, 2H, J = 7.8 Hz), 7.64 (t, 1H, J = 7.6 Hz), 8.08 (brd, 2H, J = 7.7 Hz).

5c: R_f 0.40 (hexanes/EtOAc, 3/1); IR (KBr) 3449 (br), 3082, 2981, 1745, 1696, 1611, 1574, 1449, 1372, 1336, 1280, 1121, 1063, 984, 830, 751, 683 cm^{-1}; ^1H NMR δ 1.46 (s, 9H), 5.13 (brs, 2H), 6.91 (d, 1H, J = 16.2 Hz), 7.42-7.45 (m, 3H), 7.58-7.59 (m, 2H), 7.90 (d, 1H, J = 16.2 Hz).

5d: R_f 0.42 (hexanes/EtOAc, 2/1); IR (KBr) 3465 (br), 3419 (br), 2990, 2941, 1728, 1699, 1625, 1447, 1372, 1311, 1277, 1122, 1036, 833, 802, 750 cm^{-1}; ^1H NMR δ 1.46 (s, 9H), 1.99 (s, 3H), 2.26 (s, 3H), 5.11 (brs, 2H), 6.17 (s, 1H).

5e: R_f 0.43 (hexanes/EtOAc, 2/1); IR (KBr) 3437 (br), 2980, 2931, 1733 (br), 1638, 1396, 1371, 1258, 1152, 914, 840 cm^{-1}; ^1H NMR δ 1.49 (s, 9H), 2.42 (q, 2H, J = 6.8 Hz), 2.68 (t, 2H, J = 7.2 Hz), 4.98 (brs, 2H), 5.01 (dd, 1H, dd, 1H, J_1 = 10.2 Hz, J_2 = 1.6 Hz), 5.07 (dd, 1H, J_1 = 17.2 Hz, J_2 = 1.6 Hz), 5.75-5.80 (m, 1H).

5f: R_f 0.30 (hexanes/EtOAc, 3/1); IR (KBr) 3442 (br), 3396 (br), 3112, 2984, 1739, 1663, 1520, 1409, 1372, 1356, 1254, 1126, 1064, 994, 810, 724 cm^{-1}; ^1H-NMR δ 1.36 (s, 9H), 5.36 (brs, 2H), 7.16 (t, 1H, J = 4.4 Hz), 7.77 (d, 1H, J = 4.8 Hz), 7.92 (brd, 1H, J = 3.6 Hz).

5g: R_f 0.47 (hexanes/EtOAc, 1/1); IR (KBr) 3426 (br), 3391 (br), 3138, 3119, 2982, 2939, 1742, 1679, 1562, 1467, 1392, 1372, 1314, 1279, 1133, 1034, 948, 888, 819, 775, 733 cm^{-1}; ^1H NMR δ 1.40 (s, 9H), 5.24 (brs, 2H), 6.61 (d, 1H, J = 2.0 Hz), 7.43 (d, 1H, J = 3.6 Hz), 7.69 (s, 1H).

5h: R_f 0.47 (hexanes/EtOAc, 1/1); IR (KBr) 3394 (br), 3062, 3006, 2980, 1751, 1732, 1702, 1460, 1372, 1311, 1240, 1134, 1095, 1028, 1011, 913, 863, 819, 721cm^{-1}; ^1H NMR δ 1.31 (s, 18H), 5.21 (brs, 4H), 8.16 (s, 4H).

Acknowledgment. This work was financially supported by the Academic Research Fund of Woosuk University in 2000.

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