



A practical procedure for the selective oxidation of phosphorus keto ylides to vicinal tricarbonyls using moist magnesium monoperoxyphthalate (MMPP) in dichloromethane at ambient temperature

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Received 2 November 2000; revised 4 December 2000; accepted 8 December 2000

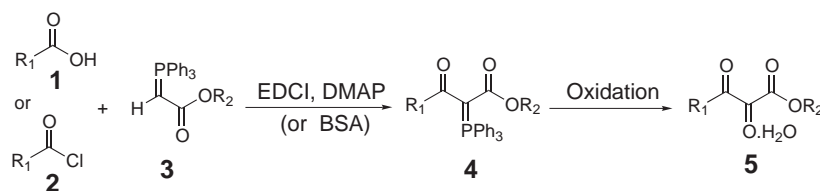
Abstract—Unsupported, moist magnesium monoperoxyphthalate (MMPP) was found to oxidize various phosphorus keto ylides to the corresponding vicinal tricarbonyls selectively in dichloromethane at ambient temperature in good to excellent yields. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of the vicinal tricarbonyl unit¹ has been an attractive and challenging research topic in recent years not only because this structural unit has been found incorporated into biologically important natural products such as FK-506,^{2a} rapamycin,^{2b} and others,^{2c,d} but also because this unit has been shown to be extremely useful for the synthesis of various heterocyclic compounds.³ Among a wide variety of synthetic methods explored,⁴ Wasserman's approach^{4c} utilizing phosphorus ylide chemistry has appeared to be one of the most elegant synthetic routes since it could introduce vicinal tricarbonyls into the target molecules^{2d,5} in a convergent way under mild conditions (Scheme 1).

For the final oxidative conversion of phosphorus keto ylides **4** to vicinal tricarbonyls **5** in Wasserman's approach, several oxidants such as oxone,^{6a} singlet oxygen,⁵ ozone,^{2d,6b} and dimethyldioxirane^{6c} have been employed. Although these oxidants have been proven

to be very useful, there are some limitations associated with these reagents, such as heterogeneous reaction conditions, use of specific equipment to generate oxidant, functional group incompatibility, necessitating careful control of reaction conditions, or unavailability from commercial sources.

We have recently reported that *m*-chloroperoxybenzoic acid (*m*-CPBA) readily oxidizes a carbon–phosphorus double bond selectively in the presence of a number of other oxidizable functional groups under mild conditions (–25°C, 2.3–2.4 equiv. of *m*-CPBA, 1.5–2.0 h, 76–96%).⁷ *m*-CPBA, however, suffers from several drawbacks in terms of cost, safety, and operational simplicity.⁸ Therefore, we envisioned that magnesium monoperoxyphthalate (MMPP),⁹ a cheap, safe and commercially available alternative to *m*-CPBA, could be utilized for this oxidative conversion. Although MMPP has been used in a number of different types of



Scheme 1.

Keywords: phosphorous ylide; oxidation; vicinal tricarbonyl; magnesium monoperoxyphthalate (MMPP); dichloromethane; ambient temperature.

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oxidations, those reactions are generally carried out in water or a low molecular weight alcohol owing to its low solubility in organic solvents.⁹ On the other hand, a modification of MMPP, i.e. unsupported, moist MMPP¹⁰ has recently been shown to be highly effective for the oxidation of sulfides to sulfoxides in dichloromethane. Herein, we wish to report preliminary results on the selective oxidation of phosphorus keto ylides to vicinal tricarbonyls using unsupported, moist MMPP in dichloromethane at ambient temperature. The representative results are summarized in Table 1.

Phosphorus keto ylide **4a** was chosen as a starting material for optimization of reaction conditions since many biologically important natural products incorporating tricarbonyls also contain alkene and carbonyl groups that have been known to undergo epoxidation and Baeyer–Villiger oxidation with MMPP in aqueous media.¹¹ Thus, when **4a** was stirred with 1.0 equivalent of moist MMPP¹² in dichloromethane at rt for 8 h, tricarbonyl **5a** was obtained in 85% yield together with recovered starting material (ca. 3–4%) (entry 1). With a slight stoichiometric excess of MMPP (1.05 equiv.), oxidation of **4a** to tricarbonyl **5a** was complete in 4 h in

Table 1. Selective oxidation of phosphorus keto ylides to vicinal tricarbonyls using unsupported, moist^a MMPP in CH₂Cl₂ at rt¹⁹

| Entry | Phosphorus Ylides | Eq | Time (hr) | Tricarbonyls | (Yield, %) ^b |
|-------|-------------------|------|-----------|--------------|-----------------------------|
| | | | | | |
| 1 | | 1.00 | 8.0 | | 5a (85) ^c |
| 2 | | 1.05 | 4.5 | | 5a (91) |
| 3 | | 1.05 | 4.0 | | 5b (84) |
| 4 | | 1.05 | 3.5 | | 5c (85) |
| 5 | | 1.05 | 4.0 | | 5d (76) ^d |
| 6 | | 1.05 | 5.0 | | 5e (90) |
| 7 | | 2.15 | 6.0 | | 5f (79) |
| 8 | | 1.05 | 3.5 | | 5g (92) |
| 9 | | 1.05 | 4.5 | | 5h (77) ^d |

a: The optimum amount of water added was determined to be (30 μ L of H₂O/0.1 mmol, MMPP) by control experiments in which MMPP (0.1 mmol), moistened with water (10 μ L, 20 μ L, 30 μ L, 40 μ L each), was reacted with ylide **4a** (0.1 mmol), and the reaction progress of each reaction was compared qualitatively by TLC-analysis.

The larger optimum amount of water added in this oxidation compared to the reference reaction¹⁰ is probably due to the formation of tricarbonyls as hydrates.

b: Isolated yields.

c: The reaction conditions were not optimized, and ca. 3–4% of starting material (**4a**) was recovered.

d: Low yield due to the formation of unidentified, highly polar byproduct.

91% yield with no observable amount of epoxidized or Baeyer–Villiger oxidized by-products (entry 2).¹³ This result undoubtedly implies that the ylide carbon of **4a** is far more nucleophilic than the other carbons of **4a** toward the electrophilic oxygen of MMPP. The comparable high chemoselectivity was reported for the oxidation of sulfide to sulfoxide using MMPP supported on silica in dichloromethane at rt.¹⁴ Other phosphorus keto ylides (**4b,c**) with a conjugated double bond, and phosphorus keto ylide (**4d**) with an isolated double bond were also converted cleanly into their corresponding tricarbonyls (**5b,c,d**) in good yields under the similar reaction conditions (entries 3–5). The simple phosphorus keto ylide (**4e**) with an aromatic substituent was oxidized to tricarbonyl **5e** in 90% yield without an observable amount of Baeyer–Villiger oxidized by-product (entry 6). The oxidation of bis-phosphorus keto ylide **4f** is of special interest since a number of natural and synthetic substances whose cytotoxicity and antitumor/antibiotic activity is attributed to interstrand DNA cross-linking ability have been reported recently.¹⁵ Thus, bis-phosphorus keto ylide **4f** was converted into the bis-vicinal tricarbonyl **5f**, an effective interstrand DNA cross-linking agent,¹⁶ with a little excess of MMPP (79%, entry 7). In view of the fact that numerous compounds containing heterocyclic substituents exhibit biologically interesting properties,¹⁷ it is of interest to efficiently synthesize tricarbonyls with heterocyclic moieties. Thus, thiophene-substituted phosphorus keto ylide **4g** was oxidized selectively to tricarbonyl **5g** in 92% with no detectable amounts of thiophene ring- and/or *S*-oxidized by-products (entry 8). Furan-based keto ylide **4h** also afforded tricarbonyl **5h** in good yield under similar conditions. Several phosphorus keto ylides with amino acids (*N*-Cbz-Phe-, *N*-Boc-Gly-) and dipeptides (*N*-Cbz-Gly-Phe-)¹⁸ were also tested under the similar reaction conditions; however, the results were disappointing (yields <40%) apparently due to the formation of several by-products.

In conclusion, we have shown that unsupported, moist MMPP is an efficient and practical oxidant for the selective oxidation of various phosphorus keto ylides to vicinal tricarbonyls in dichloromethane at ambient temperature. Considering the advantages of MMPP, favorable reaction conditions, high selectivity, good to excellent yields, and operational simplicity, this oxidative protocol should be valuable for preparing vicinal tricarbonyls from various phosphorus keto ylides under mild conditions. Further investigation of the scope, limitations, and application of this oxidation to the synthesis of complicated molecules is underway and will be reported in due course.

Acknowledgements

Generous financial support from Woosuk University is gratefully acknowledged.

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- MMPP used in this experiment was a hexahydrate (MMPP·6H₂O, 80% purity) which was newly purchased from Aldrich Chem. Co.
- Typical experimental procedure:** MMPP (97.4 mg, 1.05 equiv.) was placed in a 30 mL dry, round-bottomed flask containing a magnetic stirring bar and fitted with a rubber septum. H₂O (47.3 μL) was added from a syringe over MMPP drop by drop, and the mixture was stirred until a thick paste was obtained (for ca. 2–3 minutes). Dry CH₂Cl₂ (1.5 mL) was added to the flask from a syringe, followed by the addition of phosphorus keto ylide **4a** (68.8 mg, 0.15 mmol). The heterogeneous mixture was stirred at rt under Ar. After complete disappearance of **4a** (4.5 h), the mixture was filtered. The solid residue was washed with CH₂Cl₂ (5 mL×3) and the washings were combined with the filtrate. Removal of the solvent under reduced pressure provided a pale-yellow oil, which was purified on Prep-TLC (SiO₂) to afford tricarbonyl **5a** as a hydrate in 91% yield. *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 (400 MHz, CDCl₃, ppm) δ 1.46 (s, 9H), 1.99 (s, 3H), 2.26 (s, 3H), 5.11 (brs, 2H), 6.17 (s, 1H).
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19. The reaction products were separated by Prep-TLC (SiO₂), and identification of each product was carried out by comparing its IR, ¹H NMR spectra with reported values. All the starting ylides and tricarbonyls are known compounds.