In Situ Generation of Ylides for Tandem Oxidation–Olefination Reactions of Unactivated Diols

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Abstract: An efficient desymmetrization of diols is achieved using phosphonium salts which undergo deprotonation in the presence of a hindered amine base and manganese dioxide to produce α,β-unsaturated hydroxy esters in good yields.

Key words: diol desymmetrization, in situ ylide generation, α,β-unsaturated hydroxy esters, lactone formation

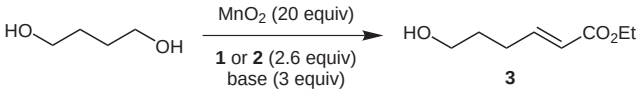
The development of tandem preparative procedures, where a number of transformations are carried out in a one-pot process, offers significant advantages such as a reduction in the number of synthetic steps and the subsequent improvement in efficiency.[1] There has been considerable recent attention in the development of such tandem sequences,[2] in particular for the direct transformation of alcohols to olefins using Wittig chemistry. The Wittig reaction remains one of the most effective synthetic methods for the introduction of a double bond, however, its utility is limited when applied to carbonyl compounds that are difficult to isolate due to their instability, toxicity, or volatility. The application of tandem oxidation−olefination circumvents these shortcomings and a range of oxidizing reagents have been employed.[3] We recently reported a highly efficient desymmetrization of unactivated diols using a manganese dioxide mediated oxidation−Wittig homologation process that produces α,β-unsaturated hydroxy esters in high yields.[4] We have now extended these studies to demonstrate that the desymmetrization process proceeds to give α,β-unsaturated hydroxy esters in tandem oxidation−olefination processes in which the ylides are generated in situ from the corresponding phosphonium salts or phosphonates and an excess of a hindered amine base.

The utilization of the guanidine bases TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) and MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) as promoters for the Wittig and Horner−Wadsworth−Emmons reactions has recently been demonstrated and provides potential improvements in efficiency.[5] Furthermore, these promoters are highly attractive due to their ease of handling and the mildness of the reaction conditions employed. Subsequently, both MTBD and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) have been successfully employed in tandem oxidation−olefination processes for the generation of ylides from a range of phosphonium salts and phosphonates in the presence of manganese dioxide, however, this methodology is limited when unactivated alcohols are employed.[6] In these cases, poor yields of product are produced even after extended reaction times at reflux temperatures. We observed in our desymmetrization studies that unactivated diols underwent tandem oxidation−olefination reactions with surprising efficiency and were intrigued to discover whether this was also the case when the ylide is generated in situ.

We initially investigated the deprotonation of phosphonium salt **1** ($Ph_3P^+CH_2CO_2EtBr^-$) and phosphonate **2** [$EtO_2P(O)CH_2CO_2Et$] with a range of bases in the presence of butane-1,4-diol and an excess of manganese dioxide. Disappointingly, our initial studies using inorganic bases, such as lithium hydroxide, or strong organic bases, such as TBD and MTBD, with phosphonium salt **1** provided only moderate yields of **3** even after extended reaction times. We were therefore highly gratified to observe that reactions utilizing triethylamine or DBU in dichloromethane proceeded to give the α,β-unsaturated hydroxy ester **3** in good yields (Table 1).

Reactions of phosphonate **2** with both inorganic and organic bases under a variety of conditions,[7] and with a range of additives, provided only moderate yields of product even when a large excess of reagents and protracted

Table 1 Tandem Oxidation–Olefination Reactions of Phosphonium Salts and Phosphonates with Butane-1,4-diol



Entry	Conditions	Time (h)	Yield (%)
1	**1**, LiOH, 4 Å MS, CH_2Cl_2, r.t.	24	33
2	**1**, TBD, CH_2Cl_2, r.t.	24	28
3	**1**, Et_3N, CH_2Cl_2, r.t.	24	61
4	**1**, DBU, CH_2Cl_2, r.t.	24	65
5	**2**, DBU, LiCl (4 equiv), CH_2Cl_2, r.t.	24	19
6	**2**, MTBD, CH_2Cl_2, r.t.	24	0
7	**2**, TBD, CH_2Cl_2, r.t.	24	20
8	**2**, LiOH, 4 Å MS, reflux, THF	8	37[a]

[a] Reaction contains 30% of the corresponding lactone product.

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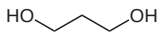
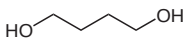
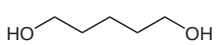
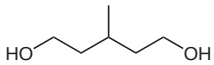
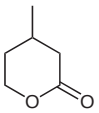
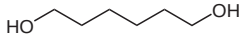
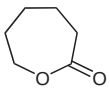
reaction times were employed. In a number of cases, the yield of **3** was limited by the production of significant quantities of lactone produced in a competing oxidative cyclization process. This lactone has been reported to undergo polymerization in the presence of catalytic quantities of strong bases such as TBD.[8] We were surprised that there is little information on the use of manganese dioxide for the oxidative cyclization of diols to lactones, given that this methodology would provide a potentially mild and simple alternative to current methodologies.[9] In addition, the generation of the lactol intermediate provides a potential explanation for the selectivity observed in the desymmetrization process. In order to clarify this point, we undertook the oxidative cyclization of symmetrical, unactivated diols to assess the efficiency of this process (Table 2).

Table 2 Manganese Dioxide Mediated Lactone Formation

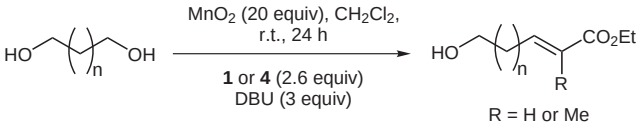
Entry	Diol[a]	Product[b]	Yield (%)[c]
1			0
2			72
3			74
4			81
5			0

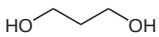
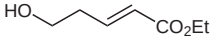
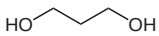
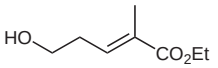
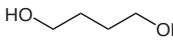
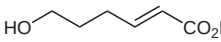
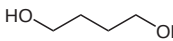
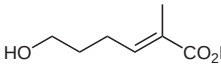
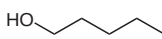
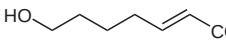
[a] All diols were used as supplied.
[b] All compounds gave satisfactory spectroscopic data.
[c] Reactions in $CHCl_3$ at reflux for 24 h using 20 equiv of MnO_2.

Reactions of butane-1,4-diol and pentane-1,5-diol in dichloromethane at room temperature in the presence of manganese dioxide gave moderate amounts of the lactones, in addition to considerable quantities of the corresponding lactols. Reactions in chloroform at reflux temperatures gave improved yields of the lactones, although considerable quantities of these products were obtained at room temperature after extended reaction times. Reactions of propane-1,3-diol and hexane-1,6-diol, however, gave no lactol or lactone products and starting material was recovered unchanged. It would appear from these studies that it is unlikely that the desymmetrization process proceeds through a lactol intermediate, given that we have previously demonstrated that these diols undergo tandem oxidation−olefination efficiently to produce the corresponding α,β-unsaturated hydroxy ester products.[4] It would also appear that the oxidation−olefination reactions involving the phosphonate **2** are limited in their efficiency due to the low quantities of ylide generated under the reaction conditions. This is insufficient to trap all of the carbonyl intermediate, either in its cyclic or acylic form[10] as the olefin product, which instead undergoes a second oxidation process to give the lactone which is unreactive toward the ylide.[11] Thus, the low yields of product observed in reactions utilizing extended reaction times or elevated temperatures can also be explained by the oxidation reaction being favored over the olefination reaction.

We next considered the oxidation−olefination reaction of a range of simple, unactivated diols which underwent efficient desymmetrization with the phosphonium salts **1** and **4** [$Ph_3P^+CH(CH_3)CO_2EtBr^-$] to produce the corresponding α,β-unsaturated hydroxy esters in good yield (Table 3).

Table 3 Synthesis of α,β-Unsaturated Hydroxy Esters from Phosphonium Salts



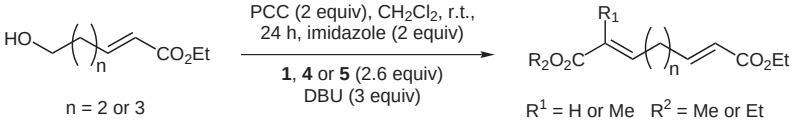
Entry	Diol	Product[a,b]	Yield (%)[c]
1			68
2			65
3			65
4			81
5			69[d]

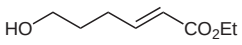
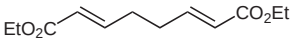
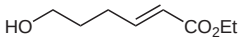
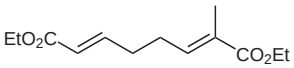
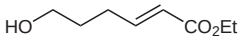
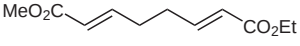
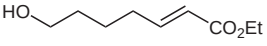
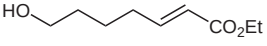
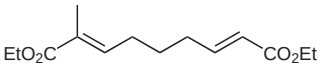
[a] Reactions using Aldrich 10 μm MnO_2.
[b] Reactions produced ca. 5% *Z*-isomer.
[c] Reactions produced ca. 5% diester.
[d] Reaction at reflux.

We also considered the synthesis of the corresponding dienyl diesters using the sequential PCC oxidation−Wittig process we previously reported.[4] Reactions involving DBU and phosphonium salts **1**, **4**, or **5** ($Ph_3P^+CH_2CO_2MeBr^-$) in the presence of silica-supported PCC produced both symmetrical and unsymmetrical dienyl diesters in good yields (Table 4). Using this approach, it was also possible to generate unsaturated products derived from unstable Wittig reagents, although yields did not exceed 20% in the cases studied to date.[12]

In summary, we have demonstrated that the desymmetrization of unactivated diols proceeds to give α,β-unsaturated hydroxy esters in good yields in reactions where the ylide is generated in situ from the corresponding phosphonium salt and an amine base. Low yields of α,β-unsaturated hydroxy esters are produced in reactions utilizing phosphonates but are limited by a competing oxidative cy-

Table 4 PCC-Mediated Synthesis of Dienyl Diesters from Phosphonium Salts



Entry	Reactant	Product	Yield (%)[a]
1			83
2			73
3			84
4			78
5			61

[a] Reactions produced ca. 5% *E,Z*-isomer.

clization of the diol to the lactone. Finally, α,β-unsaturated hydroxy esters are converted into the corresponding dienyl esters in a sequential reaction sequence utilizing PCC as the oxidant in the presence of DBU and phosphonium salts.

Typical Procedure for the Desymmetrization of Diols by in Situ Generation of the Wittig Reagent: (*E*)-5-Hydroxypent-2-enoic Acid Ethyl Ester

A mixture of propane-1,3-diol (142 mg, 1.87 mmol), (ethoxycarbonylmethylene)triphenylphosphonium bromide 1 (2.6 equiv, 2.09 g, 4.86 mmol), DBU (3 equiv, 0.89 g, 5.61 mmol) and MnO_2 (20 equiv, 3.26 g, 37.4 mmol) in CH_2Cl_2 (50 mL) was stirred for 24 h at r.t. At this time, the MnO_2 was removed by filtration through a Celite pad, which was then washed with additional CH_2Cl_2 (2 × 10 mL). The solvent was then removed to give an orange oil which was purified by column chromatography (hexane → 20% EtOAc−hexane) to give the title compound (177 mg, 68%) as a colorless oil. IR (film/neat): ν_{max} = 3422, 1714, 1653, 1267, 1162, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (3 H, t, *J* = 7 Hz), 2.20 (1 H, br s, OH), 2.46 (2 H, dq, *J* = 7, 1 Hz), 3.76 (2 H, t, *J* = 7 Hz), 4.20 (2 H, q, *J* = 7 Hz), 5.91 (1 H, dt, *J* = 16, 1 Hz), 6.95 (1 H, dt, *J* = 16, 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 145.8, 123.9, 61.3, 60.8, 35.8, 14.6. MS (ES, NH_3): *m/z* = 162 $[M + NH_4]^+$, 145 $[M + H]^+$. HRMS (ES, NH_3): *m/z* calcd for $C_7H_{16}O_3N$: 162.1125 $[M + NH_4]^+$; found: 162.1124 $[M + NH_4]^+$.

Typical Procedure for the Oxidative Cyclization of Diols: 4-Methyltetrahydropyran-2-one

A mixture of 3-methylpentane-1,5-diol (243 mg, 2.06 mmol), MnO_2 (20 equiv, 3.58 g, 41.2 mmol) in $CHCl_3$ (10 mL) was stirred at reflux for 24 h. At this time, the manganese dioxide was removed by filtration through a Celite pad, which was then washed with additional $CHCl_3$ (2 × 10 mL) The solvent was then removed to give the title compound (190 mg, 81%) as a colorless oil. IR (neat): ν_{max} = 2959, 1724, 1402, 1256, 1224, 1088, 1062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00 (3 H, d, *J* = 7 Hz), 1.40−1.52 (1 H, m), 1.81−1.90 (1 H, m), 1.98−2.08 (2 H, m), 2.56−2.66 (1 H, m), 4.16−4.24 (1 H, m), 4.32−4.39 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 69.0, 38.7, 31.0, 27.0, 21.9. MS (CI, NH_3): *m/z* = 115 $[M + H]^+$, 133 $[M + NH_4]^+$. HRMS (CI, NH_3): *m/z* calcd for $C_6H_{11}O_2$: 115.0754 $[M + H]^+$; found: 115.0754 $[M + H]^+$.

Typical Procedure for the PCC-Mediated Synthesis of Dienyl Diesters: (*E,E*)-Octa-2,6-dienedioic Acid Diethyl Ester

A mixture of (*E*)-6-hydroxyhex-2-enoic acid ethyl ester (**3**, 146 mg, 0.92 mmol) and PCC (2 equiv, 0.40 g, 1.84 mmol, ground with 2 weight equiv of silica, 0.80 g) was stirred for 4 h at r.t. in CH_2Cl_2 (50 mL). Imidazole (2 equiv, 0.13 g, 1.84 mmol) was added and the reaction mixture stirred for a further 1 h. The addition of (ethoxycarbonylmethylene)triphenylphosphophosphonium bromide **1** (2.6 equiv, 1.05 g, 2.39 mmol) and DBU (3 equiv, 0.42 g, 2.76 mmol) was followed by 19 h of stirring. At this time, the silica-supported PCC was removed by filtration through a Celite pad, which was then washed with additional CH_2Cl_2 (2 × 50 mL). The solvent was then removed to give an orange–brown oil which was purified by column chromatography (hexane → 10% EtOAc−hexane) to give the title compound (174 mg, 83%) as a colorless oil. IR (film/neat): ν_{max} = 2982, 1714, 1654, 1368, 1265, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (6 H, t, *J* = 7 Hz), 2.35−2.40 (4 H, m), 4.18 (4 H, q, *J* = 7 Hz), 5.84 (2 H, d, *J* = 16 Hz), 6.90−6.95 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 147.3, 123.0, 60.7, 30.8, 14.6. MS (CI, NH_3): *m/z* = 244 $[M + NH_4]^+$, 227 $[M + H]^+$. HRMS (CI, NH_3): *m/z* calcd for $C_{12}H_{22}O_4N$: 244.1543 $[M + NH_4]^+$; found: 244.1542 $[M + NH_4]^+$.

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