Regioselective C-Acylation of Vinylphosphorus Compounds Through Electroreduction or Mg-Promoted Reduction

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Abstract: Either of electroreduction or Mg-promoted electron-transfer reaction of vinylphosphonate derivatives **1**-**4** in the presence of acid anhydrides **5a-c** or acid chlorides **15b,c** brought about regioselective C-acylation to give the corresponding β-acylphosphonates **3** in good yields. The reaction may be initiated through one-electron transfer from either a cathode or Mg metal to a substrate to give the corresponding anion radical, which is then subjected to electrophilic attack of an acylating agent, followed by the fast second electron-transfer.

Key words: vinylphosphonates, electron-transfer, acylations, magnesium, cross-coupling

It was found by us and other groups that electroreduction of activated olefins, such as α,β-unsaturated esters and nitriles, in the presence of acid anhydrides brought about regioselective C-acylation to give the corresponding β-acylated products in good yields.[1–3] On the other hand, phosphorus compounds are of much usefulness as medicines, agrochemicals, plasticizers, fire retardants and heavy metal extraction agents because of their interesting properties and easy availability. Therefore, selective C-acylation using phosphonates or phosphine oxides as active electron-withdrawing groups of electron-deficient olefins may be an important and challenging subject in synthetic transformation.

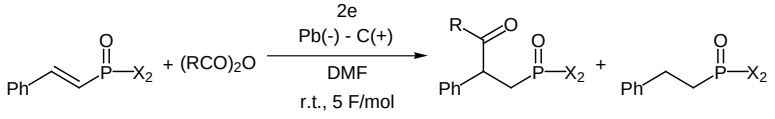
In this study, we wish to report on facile and regioselective C-acylation of vinylphosphonate derivatives by either electroreduction or Mg-promoted reduction in the presence of acylating agents to give the corresponding β-acylated products in good yields. The starting vinylphosphonates **1**-**3**[4a–e] and phosphine oxide **4**[5] were prepared according to literature procedures[6] (Scheme 1).

The electroreduction of starting substrates **1**-**4** was carried out using a divided cell equipped with a lead plate as the cathode and a carbon rod as the anode in the presence of a large excess of acid anhydride **5a**,**b** in DMF containing tetraethylammonium *p*-toluenesulfonate as a supporting electrolyte until 5 F/mol of electricity passed through the system. The corresponding β-acylated phosphonates **6**-**8**[7] or phosphine oxide **9** were obtained in good yields, accompanied with a small amount of simply reduced products **10**-**13** as by-products, as shown in Table 1. Extremely low yield of γ-keto-phosphonates **8b** from diphenyl phosphonate **3** may be elucidated by easy hydrolysis of the substrate and/or the product during the electroreduction, since phenol was obtained as the main product.

Table 1 Electroreduction of Compounds **1**-**4**

Entry	Substrate	R	Conv. (%)	Yield (%)
1	**1**	**5a**: Me	94	**6a**: 56 **10**: 13
2	**1**	**5b**: Et	100	**6b**: 41 **10**: -
3	**2**	**5b**: Me	85	**7a**: 46 **11**: 9
4	**2**	**5b**: Et	100	**7b**: 72 **11**: 7
5	**3**	**5b**: Et	75	**8b**: 5 **12**: 4
6	**4**	**5b**: Et	90	**9b**: 60 **13**: 18

Reaction Conditions: Anode: lead, Cathode: carbon, Substrate (4 mmol), Acylating agents (60 mmol), Et_4NOTs (40 mmol), DMF (30 mL), Temp.: r.t., Current Density (5 mA/cm^2), Divided cell, Electricity (5 F/mol), under nitrogen atmosphere.



1 : X = OEt
2 : X = O*i*Pr
3 : X = OPh
4 : X = Ph

5a : R = Me
5b : R = Et

6 : X = OEt
7 : X = O*i*Pr
8 : X = OPh
9 : X = Ph

10 : X = OEt
11 : X = O*i*Pr
12 : X = OPh
13 : X = Ph

Scheme 1

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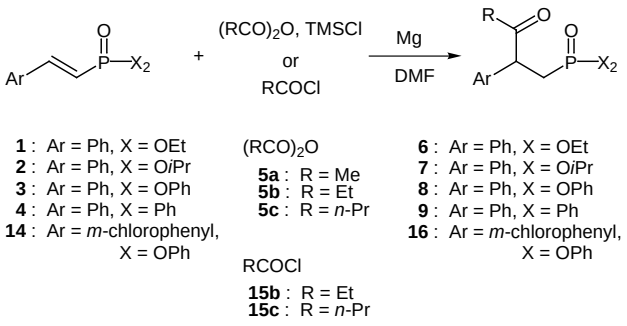
Furthermore, Mg-promoted acylation of (2-phenylethenyl)phosphonates **1**-**3,** phosphine oxide **4** and [2-(*m*-chlorophenyl)ethenyl]phosphonates **14** with acylating agents was found to give the similar results to those from the electrochemical method (Scheme 2). Thus, the reaction of **1**-**4** with acid anhydrides **5a-c** (15 equiv) in the presence of TMSCl (or acid chlorides **15** in the absence of TMSCl) in DMF took place in the presence of Mg turnings (6.0 equiv) for Grignard reaction without any pretreatment to give smoothly the corresponding β-acylated product **6**-**9**[8] and **16,** respectively, in moderate to good yields accompanying with no simply reduced products **10**-**13** (Table 2).



Scheme 2

The reaction did not proceed at all in the absence of Mg-metal, and the absence of TMSCl in the reaction using acid anhydrides resulted in incomplete consumption (18%) of the substrate even after 68 hours (Table 2, entry 2). It was assumed that TMSCl played a critical role for the continuous activation of the Mg metal surface as a weak Lewis acid. Use of acid chloride **15** as an acylating agent instead of the acid anhydrides **5**/TMSCl system also led to smooth proceeding of the reaction since Mg metal was also activated by acid chloride.

It is interesting that the present Mg-promoted C-acylation of diphenyl phosphonate **4** gave satisfactory results (entries 8 and 14), showing a sharp contrast with the results from electroreduction.

The reaction of diethyl β-cyanovinylphosphonate **17**,[9] bearing a nitrile group instead of a phenyl group, gave a geometric isomer of the enol ester **18** in a 30% yield (Scheme 3). This phenomenon may indicate some scope and limitation of the present C-acylation.[10]

The Mg-promoted coupling of chiral (*R*)-1,1′-binaphthyl phosphonate **19**[11] with propionic anhydride in DMF afforded a complex mixture (Scheme 4, Table 3, entry 1). However, use of acetonitrile and DMSO as solvent afforded the corresponding β-acylated phosphonate **20** in 36% and 56% yields, showing low diastereoselectivities (14 d.e. and 17 d.e., respectively).

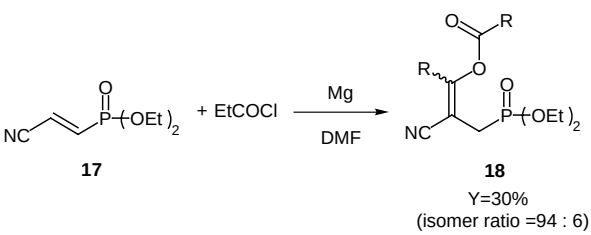
The following scheme may be proposed as a reaction mechanism for both of the present regioselective C-acylations of vinylphosphonates **1**-**4** (Scheme 5). The reaction may be initiated through one-electron transfer from cathode or Mg-metal to the substrates to give the corresponding anion radicals. These anion radicals may be then subjected to electrophilic attack of the acylating agents, followed by the fast second electron-transfer to give the carbanion species, which are protonated to give the final products.

Table 2 C-Acylation of Vinylphosphorus Compounds **1**-**4**, **14**

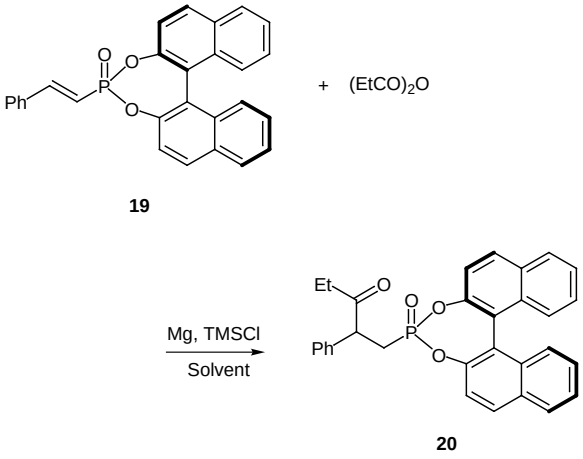
Entry	Substrate	Acylating Agent	TMSCl	Yield (%)
1	**1**	**5a** $(MeCO)_2O$	1equiv	**6a**: 45
2	**1**	**5a** $(MeCO)_2O$	-	**6a**: 45[a]
3	**1**	**5b** $(EtCO)_2O$	1equiv	**6b**: 65
4	**1**	**5c** $(n\text{-}PrCO)_2O$	1equiv	**6c**: 62
5	**2**	**5a** $(MeCO)_2O$	1equiv	**7a**: 64
6	**2**	**5b** $(EtCO)_2O$	1equiv	**7b**: 50
7	**2**	**5c** $(n\text{-}PrCO)_2O$	1equiv	**7c**: 77
8	**3**	**5b** $(EtCO)_2O$	1equiv	**8b**: 51
9	**4**	**5b** $(EtCO)_2O$	1equiv	**9b**: 46
10	**1**	**15b** EtCOCl	-	**6b**: 56
11	**2**	**15b** EtCOCl	-	**7b**: 61
12	**2**	**15c** *n*-PrCOCl	-	**7c**: 61
13	**3**	**15b** EtCOCl	-	**8b**: 74
14	**4**	**15b** EtCOCl	-	**9b**: 53
15	**14**	**15b** EtCOCl	-	**16b**: 68

Reaction Conditions: Substrate (4 mmol), Acylating agents (60 mmol), TMSCl (4 mmol), Mg (24 mmol), DMF (50 mL), Temp. –10 °C to r.t., 9 h, under nitrogen atmosphere.
[a] Stirred for 68 h (Conv. = 82%).

As a conclusion, facile and regioselective acylation on the β-carbon atom of aromatic vinylphosphonate derivatives **1**-**4** was successfully accomplished by either electroreduction or Mg-promoted electron-transfer reaction to give the γ-ketophosphonates in good yields, which were formed by conjugated nucleophilic attack of difficultly available acyl anions or their chemical equivalents to **1** (Scheme 5). The presence of a phosphonate group on a



Scheme 3



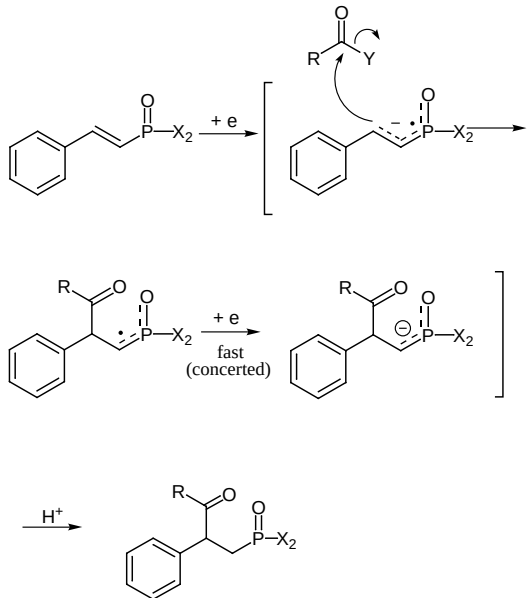
Scheme 4

Table 3 Solvent effect on Yield and Diastereoselectivity in C-Acylation of **19**

Entry	Solvent	Yield (%)[a]	d.e. (%)
1	DMF	complex mixture	
2	CH_3CN	36	17
3	DMSO	56	14

Reaction Conditions: Substrate (4 mmol), Acylating agents (60 mmol), TMSCl (4 mmol), Mg (24 mmol), DMF (50 mL), Temp. –10 °C to r.t., 9 h, under nitrogen atmosphere.
[a] Isolated yield.

styrene moiety activates an olefinic bond for an electron-transfer type of reductions, and also provides new types of phosphorus-containing functional materials.



Scheme 5

References and Notes

(1) (a) Ohno, T.; Aramaki, H.; Nakahiro, H. *Tetrahedron* **1996**, *52*, 1943. (b) Ohno, T.; Nakahiro, H.; Sanemitsu, K.; Hirashima, T.; Nishiguchi, I. *Tetrahedron Lett.* **1992**, *33*, 5515.

(2) (a) Shono, T.; Nishiguchi, I.; Ohmizu, H. *J. Am. Chem. Soc.* **1977**, *99*, 7396. (b) Lund, H.; Degrand, C. *Tetrahedron Lett.* **1977**, *18*, 3597. (c) Degrand, C.; Mons, R.; Lund, H. *Acta Chem. Scand.* **1983**, *37B*, 429. (d) Kise, N.; Hirata, Y.; Hamaguchi, T.; Ueda, N. *Tetrahedron Lett.* **1999**, *40*, 8125.

(3) (a) Haubeeb, J. J.; Tuck, D. G. *J. Chem. Soc., Chem. Commun.* **1976**, 696. (b) d'Incan, E.; Sibille, S.; Perichon, J.; Moingecon, M. O.; Chaussard, J. *Tetrahedron Lett.* **1986**, *27*, 4175.

(4) (a) Hirao, T.; Masunaga, T.; Yamada, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909. (b) Tavs, P.; Korte, F. *Tetrahedron* **1967**, *23*, 4677. (c) Griffin, C. E.; Mitchell, T. D. *J. Org. Chem.* **1965**, *30*, 1935. (d) Axelrad, G.; Laosooksathitand, S.; Engel, R. *J. Org. Chem.* **1981**, *46*, 5200. (e) Kabachnik, M. I.; Medved, T. Y.; Matrosov, E. I. *Dokl. Akad. Nauk SSSR* **1965**, *162(2)*, 339.

(5) Aguiar, A. M.; Daigle, D. *J. Org. Chem.* **1965**, *30*, 2826.

(6) All the starting substrates in this study were determined to possess *E* configuration by ^1H NMR analysis.

(7) **Typical Procedure for electrolysis of vinylphosphonate derivative 2**: In a 50 mL of beaker-type undivided glass cell equipped with a carbon rod as the anode and a lead plate as the cathode were introduced 30 mL of anhyd DMF as a solvent, Et_4NOTs (10.8 g, 40 mmol) as a supporting electrolyte, propionic anhydride **5b** (60 mmol) and vinylphosphonates **2** (4 mmol). The electrolysis was carried out under constant current conditions (current density: 5 mA/cm^2) with magnetic stirring until 5 F/mol of electricity was passed. After the electrolysis, the reaction mixture was poured into sat. aq $NaHCO_3$ solution and extracted with ether. The organic layer was successively washed with brine and dried ($MgSO_4$). After removal of the drying agent by filtration, the solvent was evaporated by distillation. The residue purified by flash column chromatography on silica gel using AcOEt–*n*-hexane (1/3 to 3/1). **7a**: Y = 72%; IR (neat, cm^{-1}): 2970, 1720, 1500, 1450, 1380, 1250, 1100, 1000, 700; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.23 (m, 5H, Ph-), 4.66-4.51 (m, 2H, P-O-CH), 4.08 (td, 1H, J_{HH} = 6 Hz, J_{PH} = 12.7 Hz, P-C-CH), 2.72 (ddd, 1H, J_{HH} = 6 Hz, J_{PH} = 15.5 Hz, J_{gem} = 17.7 Hz, PCH_2), 2.09 (s, 3H, J_{PH} = 4.4 Hz, $C(O)CH_3$), 2.03 (ddd, 1H, J_{H1H2} = 6 Hz, J_{PH} = 15.5 Hz, J_{gem} = 17.7 Hz, PCH_2), 1.27 (d, 3H, J_{HH} = 5.9 Hz, O-C-CH_3), 1.23 (d, 3H, J_{HH} = 5.9 Hz, O-C-CH_3), 1.22 (d, 3H, J_{HH} = 5.9 Hz, O-C-CH_3), 1.10 (t, 3H, J_{HH} = 6.4 Hz, O-C-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.8 [d, $^3J_{PC}$ = 9.1 Hz, C(O)], 138.3 (d, $^3J_{PC}$ = 9.2 Hz, Ph^{ipso}), 129.0 (s, Ph), 128.2 (s, Ph), 127.6 (s, Ph), 70.2 (d, $^2J_{PC}$ = 7.4 Hz, P-O-C), 70.1 (d, $^2J_{PC}$ = 7.3 Hz, P-O-C), 53.5 (s, P-C-C), 29.4 (d, $^1J_{PC}$ = 143.4 Hz, PC), 28.7 [s, $C(O)CH_2$], 23.9 (d, $^3J_{PC}$ = 3.7 Hz, O-C-C), 23.8 (d, $^3J_{PC}$ = 3.7 Hz, O-C-C), 23.7 (s, O-C-C); MS (APCI) *m/z* 313 (M^++1).

(8) **Typical Procedure for Mg-promoted reduction of vinylphosphonate derivative 3 with propionyl chloride.** A solution of Mg turnings (0.59 g, 24 mmol), propionyl chloride **15b** (60 mmol) in anhyd DMF (10 mL) was stirred at –20 °C for 30 min. Then a solution of vinylphosphonate (4 mmol) in anhyd DMF (40 mL) was added dropwise to the mixture, and the resulting solution was stirred at –20 °C to room temperature for 9 h. The reaction mixture was poured into sat. aq $NaHCO_3$ solution and extracted with Et_2O. The organic layer was successively washed with brine and dried ($MgSO_4$). After removal of the drying agent by filtration, the

solvent was evaporated by distillation. The residue was purified by flash column chromatography on silica gel using AcOEt–*n*-hexane (1/3 to 3/1). **8b**: Y = 74%; IR (neat, cm^{-1}): 1720, 1600, 1490, 1270, 1220, 1190, 1160, 1030, 930, 680; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.22 (m, 9H, Ph), 7.17-7.10 (m, 4H, Ph), 6.94-6.92 (m, 2H, Ph), 4.28 (td, 1H, J_{HH} = 7 Hz, J_{PH} = 12.2 Hz, P-C-CH), 3.08 (ddd, 1H, J_{HH} = 7 Hz, J_{PH} = 16 Hz, J_{gem} = 18 Hz, PCH_2), 2.43 [m, 3H, PCH_2, $C(O)CH_2$], 0.94 [t, 3H, J_{HH} = 7 Hz, $C(O)C\text{-}CH_3$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.1 [d, $^3J_{PC}$ = 9.2 Hz, C(O)], 150.1 (d, $^2J_{PC}$ = 9.2 Hz, Ph^{ipso}), 150.0 (d, $^2J_{PC}$ = 9.1 Hz, Ph^{ipso}), 137.8 (d, $^3J_{PC}$ = 9.2 Hz, Ph^{ipso}), 129.6, 129.2, 128.2, 127.8, 125.0, 120.4, 120.3, 120.2, 52.2 (s, P-C-C), 34.5 [s, $C(O)CH_2$], 28.6 (d, $^1J_{PC}$ = 141.5 Hz, PC), 7.8 [s, $C(O)C\text{-}CH_3$]; MS (APCI) *m/z* 395 (M^++1); mp 58.5 °C.

(9) Sainz-Diaz, C. I.; Galvez-Ruano, E.; Hernandez-Laguna, A.; Bellanato, J. *J. Org. Chem.* **1995**, *60*, 74.
(10) Similar Mg-promoted reaction of non-substituted vinyl phosphonate did not give the corresponding β-acylated product.
(11) Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036.