# Hydroformylation–Amidocarbonylation of Methylvinylphosphinate. Application to Synthesis of Glufosinate

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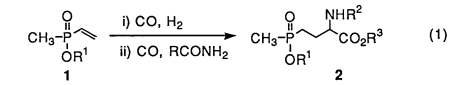
**Synopsis.** Glufosinate, 2-amino-4-[(hydroxy)methylphosphinyl]butanoic acid, (**2a**) was synthesized from 2-chloroethyl methylvinylphosphinate (**1a**) via successive hydroformylation–amidocarbonylation. Hydroformylation of **1a** catalyzed by $Co_2(CO)_8$ in methanol gave 2-chloroethyl (3,3-dimethoxypropyl)methylphosphinate (**5**). Crude **5** was subjected to cobalt-catalyzed amidocarbonylation to afford *N*-acylglufosinic acid methyl ester (**2b**). Hydrolysis of **2b** under acidic conditions gave **2a** quantitatively.

Transition metal-catalyzed carbonylations with carbon monoxide are useful methods to synthesize carbonyl compounds from easily accessible starting materials like olefins, halides, etc. Applications of these reactions to functionalized substrates are expected to provide new and facile synthetic routes to multifunctional compounds.[1] Now, we wish to report a convenient synthesis of glufosinate (**2a**) from a methylvinylphosphinate (**1a**) via successive carbonylations catalyzed by transition metal complexes (Eq. 1).

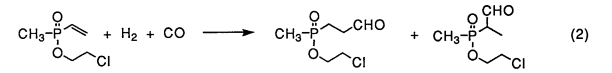



1 2

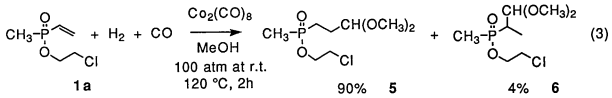
**1a**: $R^1 = CH_2CH_2Cl$ **2a**: $R^1 = R^2 = R^3 = H$
**2b**: $R^1 = CH_2CH_2Cl$, $R^2 = PhCO$, $R^3 = Me$
**2c**: $R^1 = CH_2CH_2Cl$, $R^2 = PhCO$, $R^3 = H$

Glufosinate (phosphinothricin) is the first naturally occurring amino acid with a phosphinic acid moiety and shows strong herbicidal and antibiotic activities. There have been a considerable number of precedents about the synthesis of glufosinate.[2,3] The synthetic routes are mainly divided into two categories. One is Strecker reaction of phosphinyl aldehydes.[2b-d] The other is the Michael addition of an amino acid derivative to the methylvinylphosphinate (**1**).[2e-j] The process via carbonylation (Eq. 1) is superior to these reactions in the following aspects. i) Highly toxic cyanide which requires troublesome treatment of aqueous waste is not involved. ii) The amino acid moiety is introduced inexpensively with carbon monoxide and an amide. The starting compound **1a** is easily obtained by the dehydrochlorination of 2-chloroethyl 2-chloroethylmethylphosphinate which is synthesized by the reaction of dichloromethylphosphine and ethylene oxide in a high yield.[4]

Hydroformylation of **1a** (Eq. 2) with cobalt carbonyl took place with high linear-selectivities over 85% irrespective of solvents (Table 1). However, the yield of the aldehyde was low due to the formation of high-boiling by-products. Optimization of various reaction conditions finally resulted in the finding that the reaction in methanol afforded the desired linear aldehyde in a very high yield as a form of dimethyl acetal (Eq. 3). A similar observation was reported by Wakamatsu et al. in the hydroformylation of acrylonitrile with $Co_2(CO)_8$.[5]




1a 3 4




1a 90% 5 4% 6

On the other hand, the problem in rhodium-catalyzed hydroformylation of **1a** using $Rh_4(CO)_{12}$, $Rh_2Cl_2(CO)_4$, or $HRh(CO)(PPh_3)_3$ was low linear selectivity rather than low aldehyde yield (Table 2). It is noteworthy that the high linear- or the branched-selectivities observed in

Table 1. Hydroformylation of **1a** with $Co_2(CO)_8$[a]

| Solvent | Conv./% | Yield of aldehyde/% | Linear-sel./% |
|---|---|---|---|
| Benzene | 84 | 42 | 94 |
| *t*-BuOH | 85 | 32 | 89 |
| $Et_2O$[b] | 45 | 15 | 86 |
| Acetone[c] | 21 | 15 | 92 |
| DMF | 0 | 0 | — |

a) $Co_2(CO)_8$ 0.1 mmol, **1a** 10 mmol, solvent 9 ml, 120°C, $CO/H_2=1/1$, 100 atm at room temperature, 2 h, linear-sel.=100×**3**/(**3**+**4**). b) 150°C. c) 4.5 h.

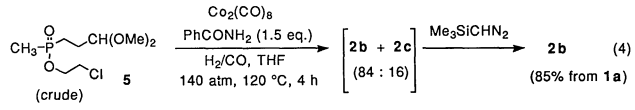
Table 2. Hydroformylation of **1a** with Rhodium Catalysts[a]

| Catalyst | Conv./% | Yield/% | | Linear-sel./% |
|---|---|---|---|---|
| | | Aldehydes | Hydrogenation | |
| $Rh_4(CO)_{12}$ | 100 | 61 | 13 | 11 |
| $Rh_2Cl_2(CO)_4$ | 100 | 70 | 19 | 22 |
| $HRh(CO)(PPh_3)_3$ | 100 | 80 | 9 | 9 |
| $Rh(acac)\{P(OPh)_3\}_2$[b] | 56 | 53 | 1 | 97 |

a) Rh 0.01 mg-atom, **1a** 10 mmol, solvent 9 ml, 100°C, $CO/H_2=1/1$, 100 atm at room temperature, 5—19 h, linear-sel.=100×**3**/(**3**+**4**). b) Rh complex 0.05 mmol, **1a** 5.7 mmol, $P(OPh)_3$ 0.13 mmol, benzene 1.4 ml, $CO/H_2=1/1$, 1 atm, 45°C, 2 h. acac: acetylacetonate.

the hydroformylation of **1a** with cobalt or rhodium catalysts, respectively, are similar to those reported for the hydroformylation of an $\alpha,\beta$-unsaturated carboxylate with $Co_2(CO)_8$ or $Rh_4(CO)_{12}$.[6] On the other hand, Trzeciak et al. have reported an unusually high linear selectivity in the rhodium-catalyzed hydroformylation of ethyl acrylate with the Rh–$P(OPh)_3$ system.[7] The catalytic system was successfully applied to the hydroformylation of **1a** to achieve a high linear selectivity under mild conditions (Table 2).[8]

Since a high linear selectivity and a high yield have been achieved in the hydroformylation of **1a** with $Co_2(CO)_8$ in MeOH (Eq. 3), we next investigated the amidocarbonylation[9] of the resulting acetal (**5**) (Eq. 4). Although examples of amidocarbonylation of acetals have been rare,[10] the reaction of **5** proceeded smoothly to give a mixture of the methyl ester (**2b**) and presumably the free carboxylic acid (**2c**);[11] the latter could be quantitatively converted to the former via the treatment with trimethylsilyldiazomethane.[12] The amidocarbonylation proceeded in various solvents such as benzene, ethyl acetate, dioxane, and tetrahydrofuran; the last one gave the highest reaction rate. Since the amidocarbonylation is slow in methanol, the solvent should be exchanged after the hydroformylation.




The hydrolysis of **2b** was easily carried out under acidic conditions to give glufosinate quantitatively. Thus, glufosinate can be efficiently synthesized via successive hydroformylation–amidocarbonylation of the methylvinylphosphinate. The resolution of racemic glufosinate and the conversion of the optical isomer to its racemate have already been established.[13]

## Experimental

$^1H$ and $^{13}C$ NMR signals were referred to tetramethylsilane as an internal standard. Chemical shift in $^{31}P$ NMR was referred to $H_3PO_4$.

$Co_2(CO)_8$ was recrystallized from toluene at a low temperature. Rh(acac)$[P(OPh)_3]_2$ was synthesized according to the literature.[14] The methylvinylphosphinate (**1a**) was obtained from Nissan Chemical Industries Ltd.

**Hydroformylation of 1a.** Octacarbonyldicobalt (0.1 mmol), the methylvinylphosphinate (10 mmol), and methanol (9 ml) were added to a 27 ml Hastelloy-C autoclave under nitrogen. Synthesis gas ($H_2/CO=1/1$) was charged up to 100 atm at room temperature. The autoclave was heated in an oil bath at 120 °C for 2 h. The reaction mixture was analyzed by capillary GC (OV-1701 and PEG-20M, 25 m) using tridecane as an internal standard. Rhodium catalyzed reactions were conducted similarly; see Table 2 for reaction conditions.

**Amidocarbonylation of 5.** Hydroformylation of **1a** was carried out in methanol as stated above. The reaction mixture was concentrated. The resulting oil, octacarbonyldicobalt (0.2 mmol), benzamide (15 mmol) and tetrahydrofuran (10 ml) were added to a 27 ml Hastelloy-C autoclave under nitrogen. Synthesis gas ($H_2/CO=1/1$) was charged up to 140 atm. The autoclave was heated in an oil bath at 120 °C for 3.8 h. The reaction mixture was analyzed by HPLC (ODS, methanol: $H_2O=1/1$) using benzene as an internal standard after the esterification of the free amino acid with trimethylsilyldiazomethane.[10]

The products were isolated by distillation (Kugelrohr) or preparative thin-layer chromatography (silica gel, $CHCl_3$: MeOH=15:1). Spectral data were listed below.

**2-Chloroethyl Methylvinylphosphinate (1a).** $^1H$ NMR[2d] ($CDCl_3$) $\delta$=1.57 (d, $J$=14 Hz, 3H, $CH_3P$), 3.70 (t, $J$=6 Hz, 2H, $CH_2Cl$), 4.0–4.4 (m, 2H, $OCH_2$), 6.0–6.5 (m, 3H, $CH=CH_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$=14.9 (d, $J$=102 Hz, $CH_3P$), 43.1 (d, $J$=7 Hz, $CH_2Cl$), 63.8 (d, $J$=6 Hz, $OCH_2$), 129.6 (d, $J$=121 Hz, $C\underline{H}=CH_2$), 135.8 (s, $CH=C\underline{H}_2$); MS $m/z$ (%) 171 ($M^+(^{37}Cl)+H$, 0.3), 169 ($M^+(^{35}Cl)+H$, 1.0), 153 ($M^+(^{35}Cl)-Me$, 4), 133 ($M^+-Cl$, 100), 119 (15), 107 (24), 91 (20). Found: $m/z$ 133.0407 ($M^+-Cl$). Calcd for $C_5H_{10}O_2P$: M, 133.0418.

**2-Chloroethyl Ethylmethylphosphinate.** Bp 80–90 °C/0.5 mmHg (1 mmHg≈133.3 Pa); $^1H$ NMR ($CDCl_3$) $\delta$=1.19 (dt, $J$=19 and 8 Hz, 3H, $C\underline{H}_3CH_2$), 1.50 (d, $J$=14 Hz, 3H, $CH_3P$), 1.80 (dq, $J$=15 and 8 Hz, 2H, $C\underline{H}_2CH_3$), 3.70 (t, $J$=6 Hz, 2H, $CH_2Cl$), 4.1–4.3 (m, 2H, $OCH_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$=6.1 (d, $J$=5 Hz, $CH_2\underline{C}H_3$), 13.2 (d, $J$=90 Hz, $CH_3P$), 22.8 (d, $J$=95 Hz, $CH_2P$), 43.4 (d, $J$=7 Hz, $CH_2Cl$), 63.7 (d, $J$=6 Hz, $OCH_2$); MS $m/z$ (%) 173 ($M^+(^{37}Cl)+H$, 0.1), 171 ($M^+(^{35}Cl)+H$, 0.3), 155 ($M^+(^{35}Cl)-Me$, 2), 141 ($M^+(^{35}Cl)-Et$, 9), 135 (100), 121 (16), 115 (14), 107 (17), 91 (54). Found: $m/z$ 171.0336 ($M^++H$). Calcd for $C_5H_{13}ClO_2P$: M, 171.0341.

**2-Chloroethyl Methyl(3-oxopropyl)phosphinate (3).** Bp 150–180 °C/0.4 mmHg; IR (neat) 1730 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) $\delta$=1.56 (d, $J$=14 Hz, 3H, CH3P), 2.10 (dt, $J$=14 and 8 Hz, 2H, $CH_2P$), 2.7–3.0 (m, 2H, $C\underline{H}_2CHO$), 3.71 (t, $J$=5 Hz, 2H, $CH_2Cl$), 4.1–4.3 (m, 2H, $OCH_2$), 9.83 (s, 1H, CHO); $^{13}C$ NMR ($CDCl_3$) $\delta$=14.5 (d, $J$=92 Hz, $CH_3P$), 21.8 (d, $J$=96 Hz, $CH_2P$), 36.1 (d, $J$=3 Hz, $\underline{C}H_2CHO$), 43.3 (d, $J$=7 Hz, $CH_2Cl$), 64.0 (d, $J$=6 Hz, $OCH_2$), 199.1 (d, $J$=13 Hz, CHO); MS $m/z$ (%) 201 ($M^+(^{37}Cl)+H$, 0.3), 199 ($M^+(^{35}Cl)+H$, 1.0), 163 ($M^+-Cl$, 21), 144 (17), 142 (48), 135 (100), 127 (24), 119 (86), 107 (100). Found: $m/z$ 199.0279 ($M^++H$). Calcd for $C_6H_{13}ClO_3P$: M, 199.0289.

**2-Chloroethyl Methyl(1-methyl-2-oxoethyl)phosphinate (4).** Bp 140–160 °C/0.35 mmHg; IR (neat) 1720 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) (diastereomer) $\delta$=1.407 and 1.423 (dd, $J$=16 and 7 Hz, 3H, $PCHC\underline{H}_3$), 1.547 and 1.569 (d, $J$=14 Hz, 3H, $CH_3P$), 3.0–3.5 (m, 1H, $C\underline{H}CHO$), 3.73 (t, $J$=5 Hz, 2H, $CH_2Cl$), 4.2–4.4 (m, 2H, $OCH_2$), 9.80 and 9.87 (d, $J$=2 Hz, 1H, CHO); $^{13}C$ NMR ($CDCl_3$) (diastereomer) $\delta$=7.61 (s, $CH\underline{C}H_3$), 7.67 (d, $J$=1.5 Hz, $CH\underline{C}H_3$), 12.77 and 12.94 (d, $J$=93 Hz, $CH_3P$), 43.06 and 43.10 (d, $J$=7 Hz, $CH_2Cl$), 50.33 and 50.39 (d, $J$=79 Hz, $\underline{C}HCH_3$), 64.51 and 64.63 (d, $J$=6 Hz, $OCH_2$), 197.77 (d, $J$=3 Hz, CHO), 197.89 (s, CHO); MS $m/z$ (%) 200 ($M^+(^{37}Cl)$, 3), 198 ($M^+(^{35}Cl)$, 11), 163 ($M^+-Cl$, 55), 149 ($M^+-CH_2Cl$, 15), 137 (15), 136 (26), 135 (100), 119 (59), 117 (13), 115 (17), 109 (42), 107 (61), 97 (24), 91 (44). Found: $m/z$ 198.0222 ($M^+$). Calcd for $C_6H_{12}ClO_3P$: M, 198.0212.

**2-Chloroethyl (3,3-Dimethoxypropyl)methylphosphinate (5).** Bp 100 °C/$5.6\times10^{-4}$ mmHg; $^1H$ NMR ($CDCl_3$) $\delta$=1.52 (d, $J$=14 Hz, 3H, $CH_3P$), 1.7–2.0 (m, 4H, $PCH_2CH_2$), 3.34 (s, 6H, $OCH_3$), 3.70 (t, $J$=6 Hz, 2H, $CH_2Cl$), 4.1–4.3 (m, 2H, $OCH_2$), 4.3–4.5 (m, 1H, $CH_2C\underline{H}$); $^{13}C$ NMR ($CDCl_3$) $\delta$=14.0 (d, $J$=92 Hz, $CH_3P$), 24.4 (d, $J$=70 Hz, $CH_2P$), 25.4 (d, $J$=21 Hz, $PCH_2\underline{C}H_2$), 43.3 (d, $J$=6 Hz, $CH_2Cl$), 53.4 (d, $J$=3 Hz, $CH_3O$), 63.8 (d, $J$=6 Hz, $OCH_2$), 104.0 (d, $J$=17 Hz, CH); MS $m/z$ (%) 245 ($M^+(^{37}Cl)-H$, 0.3), 243 ($M^+(^{37}Cl)-H$, 1.0), 231 ($M^+(^{37}Cl)-CH_3$, 6), 229 ($M^+(^{35}Cl)-CH_3$, 18), 215 ($M^+(^{37}Cl)-OCH_3$, 52), 214 (17), 213 ($M^+(^{35}Cl)-OCH_3$, 100), 199 (16), 197 (38), 193 (11), 177 (28), 165 (35), 161 (10), 151 (11), 149 (39), 141 (12), 135 (44), 133 (39), 131 (20), 121 (36), 119 (59), 107 (17), 101 (15), 93 (17). Found: $m/z$ 243.0566 ($M^+-H$). Calcd for $C_8H_{17}ClO_4P$: M, 243.0553; Found: $m/z$ 229.0398 ($M^+-CH_3$). Calcd

for $C_7H_{15}ClO_4P$: M, 229.0396.

**2-Chloroethyl (2,2-Dimethoxy-1-methylethyl)methylphosphinate (6).** This minor product formed in hydroformylation in methanol was identified only by GCMS. MS *m/z* (%) 245 ($M^+(^{37}Cl)-H$, 0.6), 243 ($M^+(^{35}Cl)-H$, 1.5), 231 ($M^+(^{37}Cl)-CH_3$, 8), 229 ($M^+(^{35}Cl)-CH_3$, 24), 215 ($M^+(^{37}Cl)-OCH_3$, 24), 213 ($M^+(^{35}Cl)-OCH_3$, 67), 199 (14), 197 (31), 177 (11), 173 (17), 165 (27), 149 (64), 143 (29), 141 (82), 135 (30), 133 (13), 125 (17), 123 (11), 117 (19), 115 (35), 111 (16), 107 (15), 102 (69), 93 (55), 79 (67), 76 (18), 75 (100). Found: *m/z* 243.0560 ($M^+$-H). Calcd for $C_8H_{17}ClO_4P$: M, 243.0553. Found: *m/z* 229.0413 ($M^+-CH_3$). Calcd for $C_7H_{15}ClO_4P$: M, 229.0396.

**2-Chloroethyl [3-Benzoylamino-3-(methoxycarbonyl)propyl]methylphosphinate (2b).** IR (neat) 3450 $cm^{-1}$ (NH), 1740 $cm^{-1}$ ($CO_2Me$), 1660 $cm^{-1}$ (PhCO); $^1H$ NMR ($CDCl_3$) (diastereomer) $\delta$=1.525 and 1.546 (d, *J*=14 Hz, 3H, $CH_3P$), 1.75–2.05 (m, 2H, $PCH_2$), 2.05–2.4 (m, 2H, $CH_2CH$), 3.6–3.75 (m, 2H, $CH_2Cl$), 3.79 (s, 3H, $CO_2CH_3$), 4.1–4.3 (m, 2H, $OCH_2$), 4.75–5.0 (m, 1H, NCH), 7.35–8.0 (m, 6H, Ph and NH); $^{13}C$ NMR ($CDCl_3$) (diastereomer) $\delta$=14.2 (d, *J*=94 Hz, $CH_3P$), 24.5 (s, $CH_2CH$), 26.01 and 26.11 (d, *J*=93 Hz, $PCH_2$), 43.27 and 43.32 (d, *J*=7 Hz, $CH_2Cl$), 52.8 (s, $CO_2\underline{C}H_3$), 52.8 (d, *J*=21 Hz, CH), 64.1 (d, *J*=7 Hz, $OCH_2$), 127.4 (s, Ph, meta), 128.6 (s, Ph, ortho), 129.9 (s, Ph, para), 133.4 (s, Ph, $C_1$), 167.4 (d, *J*=2.5 Hz, $CO_2$), 172.3 (s, PhCO); $^{31}P$ NMR ($CDCl_3$) $\delta$=55 (s); MS *m/z* (%) 363 ($M^+(^{37}Cl)$, 0.5), 361 ($M^+(^{35}Cl)$, 1.4), 304 ($M^+(^{37}Cl)-CO_2CH_3$, 19), 302 ($M^+(^{35}Cl)-CO_2CH_3$, 48), 284 (8), 256 (12), 105 (100),. Found: *m/z* 361.0865 ($M^+$). Calcd for $C_{15}H_{21}ClNO_5P$: M, 361.0845. Anal. ($C_{15}H_{21}ClNO_5P$) C, H, N, Cl.

**Hydrolysis of 2b.** The methyl ester **2b** (182 mg) was dissolved in 6 mol $dm^{-3}$ hydrochloric acid (4 ml) and refluxed overnight. The resulting mixture was washed with benzene to remove benzoic acid. The water layer was concentrated to dryness in vacuo to give pure glufosinate (**2a**) (96 mg, 100%). $^1H$ NMR[2j] ($D_2O$) $\delta$=1.42 (d, *J*=14 Hz, 3H, $CH_3P$), 1.7–2.2 (m, 4H, $PCH_2CH_2$), 4.06 (t, *J*=6 Hz, 1H, $CHCO_2$); $^{13}C$ NMR[2d,j] ($D_2O$) $\delta$=14.4 (d, *J*=92 Hz, $CH_3P$), 23.5 (d, *J*=2 Hz, $PCH_2\underline{C}H_2$), 26.0 (d, *J*=93 Hz, $PCH_2$), 53.6 (d, *J*=17 Hz, CH), 172.0 (s, $CO_2H$).

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11) Formation of a free carboxylic acid as a byproduct has been found in amidocarbonylation of an acetal.[10] Although convincing evidence to support the structure of **2c** is not available in the present experiment, the following observations are in agreement with the proposed structure. (1) The compound appeared sooner than the ester in the reversed phase HPLC. This indicates the compound is more polar than the ester. (2) Upon methylation with trimethylsilyldiazomethane, the compound disappeared and the yield of the ester consistently increased.

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