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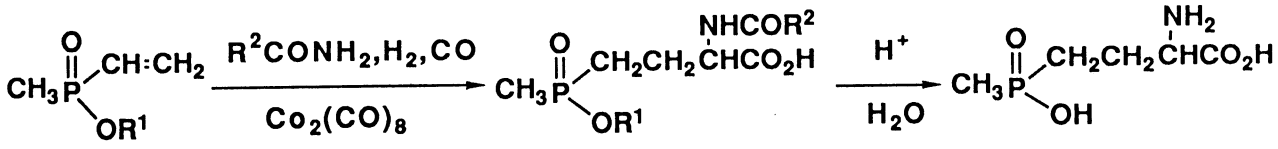
Synthesis of Glufosinate via Amidocarbonylation

Shinichiro TAKIGAWA,* Shuzo SHINKE, and Masato TANAKA *†
Central Research Institute of Nissan Chemical Industries, Ltd.,
722 Tsuboi, Funabashi, Chiba 274
† National Chemical Laboratory for Industry, 1-1 Higashi, Tsukuba, Ibaraki 305

Cobalt carbonyl-catalyzed carbonylation of methylvinylphosphinate with acetamide followed by hydrolysis gave 2-amino-4-[hydroxy(methyl)phosphinyl]-butanoic acid (glufosinate) in more than 80% overall yield.

Glufosinate, 2-amino-4-[hydroxy(methyl)phosphinyl]butanoic acid, is the first naturally-occurring phosphinyl amino acid.[1] Its derivatives exhibit biological activity such as herbicidal activity, antibiotic property, and inhibitory effect on enzymatic processes.[1,2] In particular, glufosinate itself is widely used as non-selective herbicide for foliage treatment.[3] Accordingly, the development of its synthetic process has been a subject of practical interest.[3,4] On the other hand, synthesis of N-acylamino acid by amidocarbonylation of aldehydes is well known as the Wakamatsu reaction.[5] The reaction is effected by cobalt carbonyl catalyst under similar conditions to hydroformylation. Therefore, olefins, which are in situ converted to aldehydes under the reaction conditions, can be directly subjected to the reaction.[5] We now disclose that direct amidocarbonylation of methylvinylphosphinates gives glufosinate derivatives in high yields and that the direct procedure is superior to the two stage process (hydroformylation followed by amidocarbonylation of the resulting aldehyde).[6]



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A typical procedure of the reaction was as follows. A 100 ml stainless steel autoclave was charged with acetamide (29 mmol), 2-chloroethyl methylvinylphosphinate (29 mmol), $Co_2(CO)_8$ (0.30 mmol) and dioxane (50 ml) under nitrogen atmosphere. H_2/CO gas (1/1) was introduced at 160 kg/cm^2 at ambient temperature, and the mixture was heated with stirring. When the mixture reached to 100 °C, the pressure was boosted up to 200 kg/cm^2. After stirring for 2 h at 100 °C, the reaction

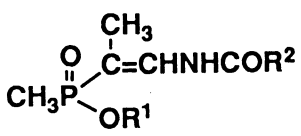
mixture was evaporated in vacuo, and the residue was refluxed with 10% aqueous HCl solution (100 ml, 3 h). The solution was evaporated and the remaining water was removed by distillation with benzene. The resulting glufosinate-HCl salt was dried in vacuo at 50 °C to give pure material [4a] in 81% yield.

Table 1. Cobalt-catalyzed Amidocarbonylation of Methylvinylphosphinates [a]

Entry	R^1	R^2	Solvent	Temp /°C	Yield of 2 /%
1	CH_3	CH_3	Dioxane	100	85
2	C_2H_5	CH_3	Dioxane	100	78
3	CH_2CH_2Cl	CH_3	Dioxane	100	82
4	CH_2CH_2Cl	CH_3	THF	100	83
5	CH_2CH_2Cl	CH_3	THF	80	73
6	CH_2CH_2Cl	C_6H_5	Dioxane	100	41

a) Total pressure 200 kg/cm^2 (H_2/CO = 1), 2 h, $Co_2(CO)_8$ 1 mol% .

Selected results are summarized in Table 1, where the yield was estimated by GLC analysis after diazomethane treatment. Except for the reaction with benzamide, we could obtain several 2-(N-acylamino)-4-[alkoxy(methyl)phosphinyl]butanoic acids in high yields. In any experiments listed in Table 1, branched analogue (2-amino-3-[hydroxy(methyl)phosphinyl]butanoic acid derivative) was not observed at all. However, we could find N-alkenylamide **4** and its hydrogeration product **4'** in 3.5-4.9% and 0.5-0.9% yield, respectively, formed in the reaction mixture. These by-products seemed to originate from the branched aldehyde **5** in situ formed as an intermediate under the direct amidocarbonylation. As a matter of fact, separately prepared branched aldehyde (R^1 = CH_2CH_2Cl) was transformed with acetamide into **4** (54%) and **4'** (10%) under amidocarbonylation conditions. On the other hand, the linear aldehyde underwent normal amidocarbonylation to give the linear N-acylamino acid **2** in 69% yield.



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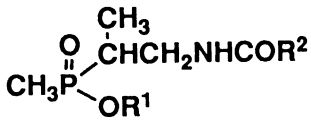
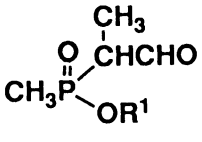


4'



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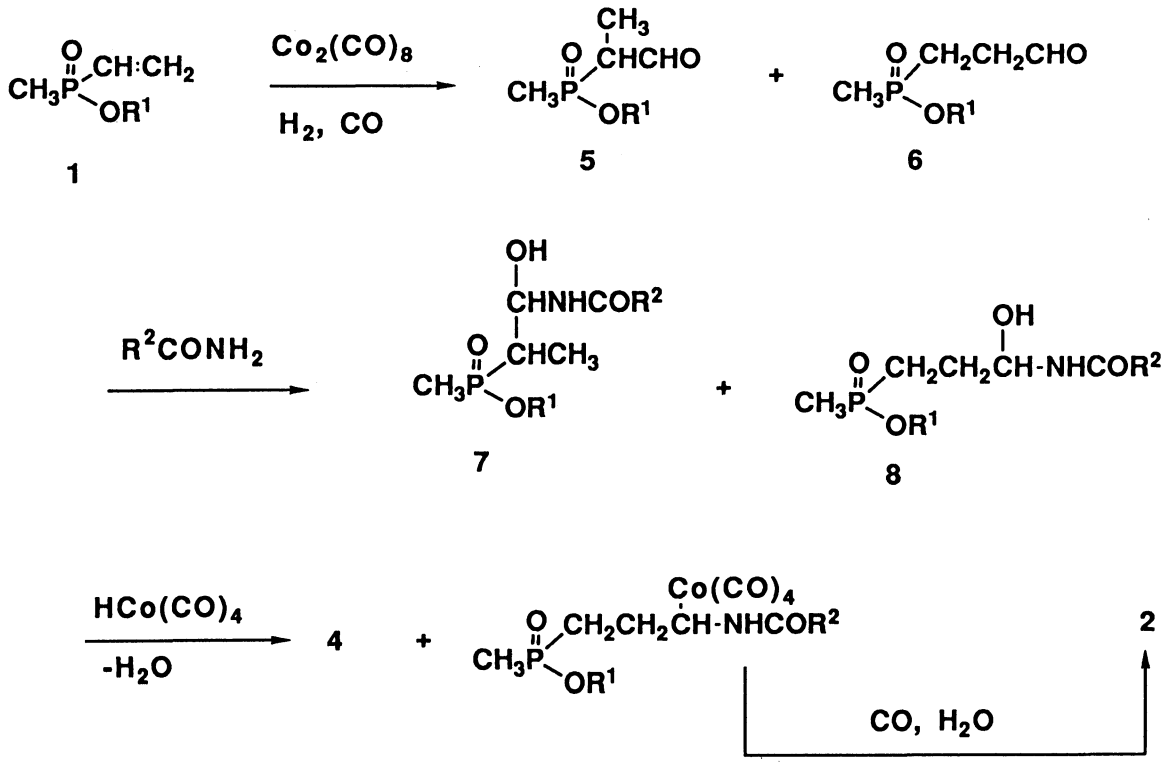
Based on these results and with reference to precedents, [5c,7] we propose the following events taking place (Scheme 1). The vinylphosphinate undergoes hydroformylation, the linear aldehyde **6**

being formed as the major isomer. High regioselectivity to linear isomers is usually encountered in cobalt-catalyzed hydroformylation of olefins which have electronegative substituents.[8] The aldehydes **5** and **6** react with amide to form hemiamidals **7** and **8**, respectively. The hemiamidal **8** reacts normally to give N-acylamino acid. However, the hemiamidal **7** is readily dehydrated to the stable alkenylamide **4**, which is reluctant to undergo carbonylation since it is a trisubstituted olefin.

To compare the direct amidocarbonylation with the two stage process, 2-chloroethyl methylvinylphosphinate was hydroformylated (phosphinate 6 mmol, $Co_2(CO)_8$ 0.12 mmol, dioxane 15 ml, 200 kg/cm^2 (H_2/CO = 1/1), 100 °C, 0.5 h). Both **5** and **6** were formed, and the **5**/**6** ratio was 13/87. This is in reasonable agreement with the foregoing proposal. However, a large amount of high boiling materials was also formed presumably because of instability of the aldehydes, and the total yield of the aldehydes was no more than 54%. This shows that the direct process which minimizes the deterioration of the aldehydes is superior to the two stage process.[9]

In summary, direct amidocarbonylation of methylvinylphosphinate followed by hydrolysis gives glufosinate in high yield. Since synthesis of methylvinylphosphinate has already been established,[10] the results herein described open up a practical process to produce glufosinate.



Scheme 1.

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