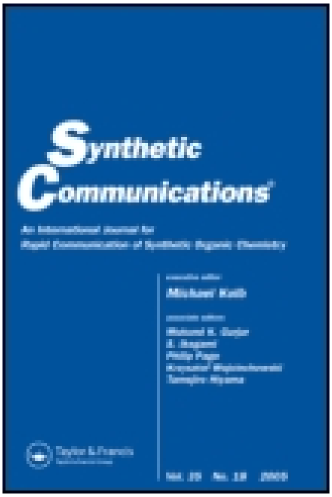

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# Solid Phase Acylation of Phosphonoacetates Synthesis of β-Keto Phosphonates from Polymer Bound Phosphonoacetate

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SYNTHETIC COMMUNICATIONS, 29(8), 1271–1275 (1999)

# SOLID PHASE ACYLATION OF PHOSPHONOACETATES : SYNTHESIS OF β-KETO PHOSPHONATES FROM POLYMER BOUND PHOSPHONOACETATE

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**Abstract :** Solid phase synthesis of phase synthesis of β-keto phosphonates, *via* acylation reaction of polymer bound phosphoacetate with carboxylic acid chlorides in the presence of magnesium chloride-triethylamine followed by cleavage of resin with concomitant decarboxylation, is described.

Combinatorial chemistry for the generation of compound libraries of large number of small molecules has been shown to be highly useful tools for accelerating lead discovery and development in pharmaceutical research.[1] Recent advances in solid phase synthesis have extended the possibility of preparing compounds by parallel synthesis and combinatorial techniques.[2]

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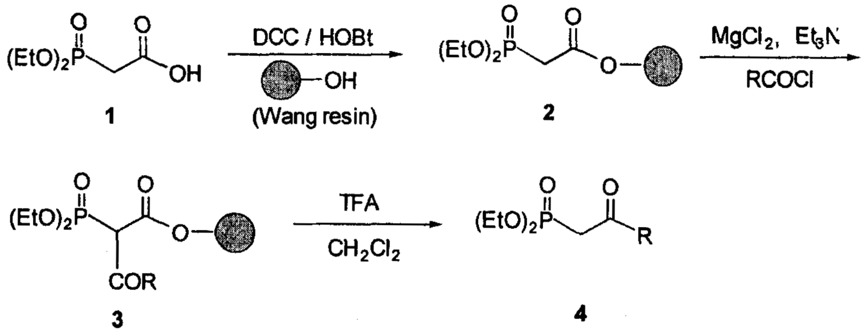
Therefore, one of the valuable challenges remains the transfer of solution phase reactions to solid phase. Active methylene compounds have been used as suitable intermediate for solid phase synthesis.[3]

We have previously reported the preparation β-keto phosphonates[4] using acylation of phosphono-acetate.[5] In this paper we describe the solid support version of this reaction to afford β-keto phosphonates *via* acylation of polymer bound phosphonoacetate. Diethyl phosphonoacetic acid **1** was attached Wang resin using DCC/HOBt coupling to give polymer bound phosphonoacetate **2**. FT-IR of the resin **2** showed the presence of phosphorus-oxygen stretches at 1243 and 1047 $cm^{-1}$. Treatment of resin **2** with carboxylic acid chlorides in the presence of magnesium chloride and triethylamine, provided acylation product **3**. Resin cleavage with concomitant decarboxylation using TFA afforded β-keto phosphonates **4** in good yields based on the resin.[6]



As shown in Table 1, the method has been applied to a number of different of carboxylic acid chlorides. The aromatic carboxylic acid chlorides reacted to give

Table 1. Preparation of β-keto phosphonates **4**.

| No | R | Yield[a](%) | No | R | Yield[a](%) |
|---|---|---|---|---|---|
| **4a** | $C_6H_5$ | 92 | **4d** | 2,4-$Cl_2$, $C_6H_3$ | 81 |
| **4b** | *p*-OMe, $C_6H_4$ | 84 | **4e** | 2,4-$Cl_2$,5-F, $C_6H_2$ | 85 |
| **4c** | *p*-Me, $C_6H_4$ | 87 | **4f** | n-pentyl | 77 |

[a] Isolated yields are based on Wang resin.

higher product yields than aliphatic carboxylic acid chloride. The aromatic carboxylic acid chlorides containing electron rich and electron deficient substituents reacted with equal efficiency. These trends are similar with reported solution phase reactions.[5]

In conclusion, we have developed the synthetic method for the solid phase preparation of β-keto phosphonates from polymer bound phosphonoacetate.

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6. General experimental procedure : To a stirred suspension of Wang resin ( 300mg, 1 mmol/g) in $CH_2Cl_2$ (10 mL), diethyl phosphonoacetic acid (**1**,

64 μL, 0.4 mmol), DCC (104 mg, 0.5 mmol), HOBt (13.5 mg, 0.1 mmol) and triethylamine (63 μL, 0.45 mmol) at room temperature, followed by stirring for 10 h. The resin **2** was washed ($Et_2O$ and EtOAc), dried. The loaded resin **2** (100 mg) was suspended in toluene (2 mL) and $MgCl_2$ (10.7 mg, 0.11 mmol), triethylamine(42 μL. 0.3 mmol) and carboxylic acid chloride (0.2 mmol) were added and stirred for 12 h at room temperature. The resin **3** was washed ($CH_2Cl_2$ and EtOAc), resuspended in 2 mL of TFA/ $CH_2Cl_2$ (1:1) for 30 min. The filtrate was pooled with resin washing ($CH_2Cl_2$ and EtOAc), concentrated, and chromatographed to give β-keto phosphonate **4**.

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