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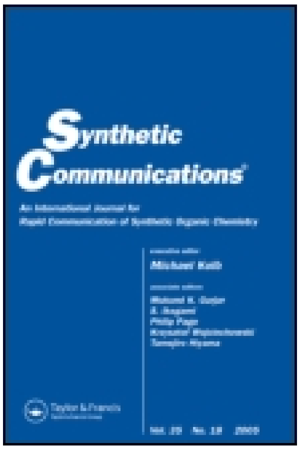

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A CONVENIENT AND MILD PROCEDURE FOR THE PREPARATION OF α-KETO PHOSPHONATES OF 1-HYDROXYPHOSPHONATES UNDER SOLVENT-FREE CONDITIONS USING MICROWAVE

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A CONVENIENT AND MILD PROCEDURE FOR THE PREPARATION OF α-KETO PHOSPHONATES OF 1-HYDROXYPHOSPHONATES UNDER SOLVENT-FREE CONDITIONS USING MICROWAVE

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ABSTRACT

The Reactions of 1-hydroxyphosphonates on the alumina-supported CrO_3 are accelerated by microwave irradiation under solvent-free conditions to afford a high yielding synthesis of α-keto phosphonates.

Phosphonic and analogues of naturally occurring phosphates have attracted considerable interest as potential regulators, mediators, or inhibitions of metabolic processes.[1] α-Ketophosphonates have a number of properties that make them attractive as reagents or intermediates for synthesis. These properties have stimulated a recent resurgence of interest in the chemistry of such compounds.[2–6] For several years it has been

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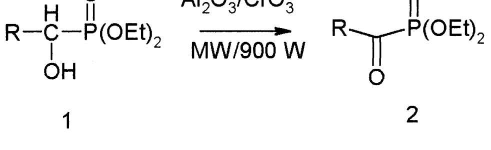
known that the carbonyl of an α-ketophosphonate is activated towards attack by nucleophiles and that the carbon-phosphorus bond is readily cleaved.[7] This property makes α-ketophosphonates potentially useful acylating agents, but also susceptible to hydrolysis and difficult to handle.[7] The chemical properties of α-ketophosphonates are mainly determined by the phosphorus substituents, but in general are hybrid between those of secondary amides and ketones.[8] For instance, it is possible to derive hydrazones, imines, and oximes from the carbonyl function;[9] or use them in witting reactions.[7a] α-Ketophosphonates are usually prepared by a Michaelis-Arbuzov reaction between a trialkyl phosphite and acid chloride.[10] The Michaelis-Arbuzov reaction works well for the less complex aroyl and alkanoyl chlorides where purification by distillation is possible. However, there has been less success in the preparation of α,β-unsaturated α-ketophosphonates where multiple addition products are often observed,[11a,b] and the products are thermally or acid sensitive compounds.[11c] An alternative method for the preparation of a-ketophosphonates is the oxidation of the corresponding hydroxyphosphonate.[12] Although there have been sporadic reports on the oxidation of hydroxyphosphoryl compounds, the reactions developed tend to work well with isolated examples, but are not usually general for arrange of substrates.

Surface-mediated solid phase reactions are of growing interest[13] because of their ease of set up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts. Acceleration of organic reactions by microwave dielectric heating has been widely exploited. Microwave irradiation in solvent-free conditions has also shown its utility in organic synthesis. As a part of our efforts to explore the utility of surface-mediated reactions,[14,15,16] in this report a new method for the preparation of α-ketophosphonates by oxidation of 1-hydroxyphosphonates on the solid surface under microwave irradiation is described. It is found that alumina (neutral)-supported CrO_3 under solvent-free conditions was capable of producing high yields of α-ketophosphonates from 1-hydroxy phosphonates under mild reaction conditions (Scheme 1, and Table 1).



Scheme 1.

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As shown Table 1, 1-hydroxyalkyl, and α,β-unsaturated phosphonates in the presence of alumina supported chromium (VI) oxide under microwave irradiation afford the desired products in excellent yields (**2a–f**). The reaction also proceeded in high yields for *o*-, *m*- and *p*-substituted 1-hydroxyphosphonates in the presence of alumina supported chromium (VI) oxide under microwave irradiation afford the desired products in excellent yields (**2g–o**). The reaction also proceeded in high yields for 1-hydroxyfurfuryl, α-naphthyl, and β-naphthyl phosphonates (**2p–r**).

The reactions are relatively clean with no tar formation, and interestingly, no cleavage of the C-P bond is observed. Indeed a wide range of 1-hydroxyphosphonates was converted to corresponding α-keto phosphonates under this condition.

In summary, simple work-up, low consumption of solvent, relatively fast reaction rates, mild reaction condition, good yields, and selectivity of the reaction make this method an attractive and a useful contribution to present methodologies.

Table 1. The Preparation of a-Ketophosphonates of 1-Hydroxyphosphonates (**1**) under Solvent-Free Condition Using Microwave Irradiation

Product **2**	**R**-	Time (min)	Yield[a] (%)
a	n-C_4H_9	2	75
b	n-C_5H_{11}-	2	76
c	$PhCH_2CH_2$-	2	78
d	$PhCHCH_3$	3	73
e	Ph-CH=CH-	1	68
f	Me-CH=CH-	1	73
g	Ph-	0.5	86
h	p-$CH_3C_6H_4$-	1	85
i	p-ClC_6H_4-	1	85
j	p-$O_2NC_6H_4$-	0.5	89
k	p-$CH_3OC_6H_4$-	1	86
l	o-ClC_6H_4-	1	80
m	o-$NO_2C_6H_4$-	1	85
n	2,4-$Cl_2C_6H_3$-	2	78
o	Furfuryl	1	75
p	α-Naphthyl	1	89
q	β-Naphthyl	1	85

[a] Isolated yields.

EXPERIMENTAL SECTION

General

All chemicals were commercial products and distilled or recrystallized before use. A kitchen type microwave at 2450 MHz (900 W) was used in all experiments. The infrared (IR) spectra were determined neat using a FTIR. ^{1}H NMR (at 500 MHz) spectra were obtained as solutions in deuteriochloroform ($CDCl_3$).

Preparation of α-Ketophosphonates (2) of 1-Hydroxyphosphonates 1. This solvent-free oxidation method is operationally simple. Thirty mmol of the reagent is prepared by the combination of CrO_3 (30 mmol, finely ground) and alumina (Al_2O_3, neutral, 5.75 g) in a mortar and pestle by grinding then together until a fine, homogeneous, orange powder is obtained (5–10 min). The 1-hydroxyphosphonate[17] (10 mmol) was added to this reagent and was irradiated by microwave. The reaction mixture was washed with CH_2Cl_2 (200 mL), dried (Na_2SO_4), and the solvent evaporated to give the crude products. Pure product was obtained by distillation under reduced pressure in 65–90% yields.

Acylphosphonates 2. All products gave satisfactory spectral data in accord with the assigned structures and literature reports.[7] [E.g. for **2g** ^{1}H NMR ($CDCl_3$, TMS) δ: 1.22 (t, 3H, $J = 6$ Hz, -OCH_2CH_3), 1.23 (t, 3H, $J = 6$ Hz, -OCH_2CH_3), 4.05–4.72 (m, 4H, -OCH_2CH_3), 7.28 (t, 2H, $J = 7.3$ Hz), 7.54 (t, 1H, $J = 7.3$ Hz), 8.18 (d, 2H, $J = 7.3$ Hz); IR (neat): ν 1659 (C = O), 1610 (Ar), 1258 (P = O), 1103–1025, 978 (P-O-Et) cm^{-1}].

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17. Procedure for the preparation of 1-hydroxyphosphonates (**1**): Magnesium oxide (2 g) was added to a stirred mixture of diethyl phosphite (0.02 mol) and aldehyde (0.02 mol) at room temperature. After 2 h the mixture was washed by dichloromethane (4×50 mL) and dried with $CaCl_2$; evaporation of the solvent gave the crude product. The products were crystallized from CH_2Cl_2/*n*-hexane (1:2) or distillated under reduced pressure.

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