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A quantitative synthesis of β-carboxylated thiolophosphates via a Michael reaction

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Abstract—Reactions of *O*,*O*′-dialkylthiophosphoric acids with acrylates provide a direct synthetic route to β-carboxylated thiolophosphates. This Michael addition, without solvent, is quantitative at 90°C in 1 h for the 2/1 thiophosphoric acid/acrylate ratio. Moreover, this excess of thiophosphoric acid can be reused for further reactions.

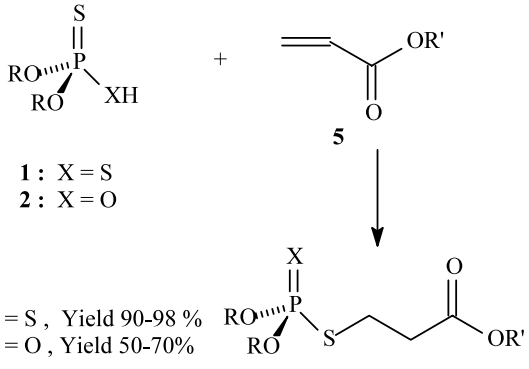
O,*O*′-Dialkylthiophosphoric acids, thionophosphates and thiolophosphates have been the subject of a number of studies about various uses involving organic synthesis intermediates,[1] biochemistry,[2] agrochemistry[3] and lubrication[4] among others. In the latter area, dithiophosphates, especially their zinc salts (ZDTPs), are used for their anti-wear, anti-corrosion and extreme pressure properties.[5] But recent studies have revealed allergic contact dermatitis from ZDTPs[6] and toxic and mutagenic effects of these additives due to the presence of zinc.[7] Previously, we have shown that *O*,*O*′-dialkyldithiophosphates with a carboxylate function can be suitable additives without zinc.[8] A simple way to synthesize β-carboxyl compounds **3** in good yields (80–95%), is to react dithiophosphate **1** with acrylate **5** (Scheme 1). However, if this Michael reaction is carried out with thiophosphoric acid **2**, the reaction is not complete (conversion 70%). In the present study, we report the reactivity of *O*,*O*′-dialkylthiophosphoric acids towards acrylates and a simple and convenient synthesis to obtain **4** quantitatively.

O,*O*′-Dialkylthiophosphoric acids are obtained by the HCl hydrolysis of sodium or ammonium *O*,*O*′-dialkyl thiophosphates which are obtained by the reaction between dialkylphosphite, sodium and sulfur[9] or by the addition of sulfur on a dialkylphosphite in the presence of an amine.[10]

The Michael reaction between *O*,*O*′-diethylthiophosphoric acid **2a** and various acrylates **5** was performed without solvent, either at 90°C with MEHQ[11] to avoid polymerization (route a) or at room temperature in the presence of MEHQ and Triton® B (2%) as a catalytic base (route b).

The results in Table 1 show that these reactions give **4a**–**e** with 70% conversion, after 12 and 24 h for routes a and b, respectively. The chemical shifts in ^{31}P NMR of **4a**–**e** are consistent with those of thiolophosphates from 25 to 30 ppm.[12]

Apart from thiolophosphate **4**, thiophosphoric acid and acrylate reagents, no other product was detected, especially no thionophosphate. Although *O*,*O*′-diethylthiophosphoric acid is a potential ambident nucleophile, only its soft SH centre is reactive in this case. With a longer reaction time, not only does the conversion not increase but we also observe two other products, **6** and



Scheme 1.

Keywords: thiophosphoric acid; thiolophosphate; acrylate; Michael reaction.

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Table 1. Reaction between *O*,*O*′-diethylthiophosphoric acid and various acrylates

Product	R	R′	After 6 h[a] (Conv. %)[c]	After 12 h[a] (Conv. %)[c]	After 24 h[a] (Conv. %)[c]	After 48 h[a] (Conv. %)[c]	After 24 h[b] (Conv. %)[c]	δ ^{31}P NMR (ppm)
4a	C_2H_5	CH_3	50	68	70	70	66	26.7
4b	C_2H_5	C_2H_5	52	70	70	70	68	26.8
4c	C_2H_5	C_6H_5	55	72	72	72	70	26.7
4d	C_2H_5	$CH_2CH_2OC_2H_5$	50	68	70	70	72	26.7
4e	C_2H_5	$CH_2CH_2CH_2SC_2H_5$	50	70	70	70	66	29.3

[a] Reaction time for Route a: MEHQ, 90°C (80°C for methyl acrylate).
[b] Reaction time for Route b: MEHQ, rt, triton® B.
[c] Conversion of **2** to **4** determined by ^{1}H and ^{31}P NMR

7, in 3–7% after 12 h at 90°C (Scheme 2). After 24 h, a little polymerization of acrylate is observed also.

However, the polymerization and/or the presence of products **6**–**7** cannot merely explain why the reaction stopped at 70% conversion; all the more so as the reactions between **2a** and other Michael reagents (Table 2) led to the thiolophosphates quantitatively except with acrylonitrile (80%; in this case we noted a rapid polymerization). In the same way, the retro-Michael reaction cannot take place because **4b** is stable at 90°C for 24 h in the absence or in the presence of phenyl acrylate or benzyl bromide to trap **2a** which could be formed.

The formation at high temperature of tetraethyl dithiopyrophosphate **8** (Scheme 3), which is not reactive with acrylate, could explain the fact that the reaction stopped at 70%. This product **8** was not observed by ^{1}H, ^{13}C, ^{31}P NMR at the end of the reaction, probably because of the reverse reaction at room temperature (**8** was identified by ^{31}P NMR when a solution of **2a** in benzene was refluxed for 12 h).[13]

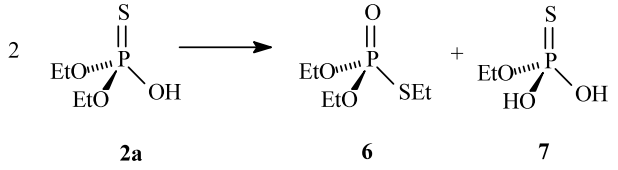
However, an experiment performed at 95°C for 30 min by thermal gravimetric analysis (TGA) using on-line FT-IR analysis of evolved gases, shows 8% of weight loss which is identified as water by FT-IR. Since the percent of initial water in the sample was 1.8% (Karl–Fischer), this result is consistent with the loss of water calculated (5.3%) and with the hypothesis relative to the formation of **8**.

Besides, the use of a solvent (ethanol, acetonitrile, THF, DMF, HMPA) and/or acid or basic catalysts at 0.05 equiv. ($AlCl_3$, CF_3COOH, C_2H_5COOH, Et_3N, Triton® B) does not increase the yield (route a). When this reaction was carried out in the presence of 0.25 equiv. of propionic acid, we observed a faster reaction (70% in 2 h) as well as the absence of **6** and **7**. Therefore, this observation suggests the use of an excess of *O*,*O*′-dialkylthiophosphoric acid **2**.

Similarly to propanoic acid, thiolophosphate is the only product and its kinetic formation is a function of the ratio of **2** (Table 3). An excess of acrylate (entries 1, 2, 10, 11) did not modify the conversion ratio of the reaction. On the contrary, an excess of **2** increased conversions from 50 to 60% for 1.5 equiv. after 1 h (entries 3, 6, 12, 13) and from 70% to 93% for 1.1 or 1.5 equiv. after 12 h (entries 5, 7, 14). The Michael addition was quantitative (conversion >98%) in 1 h for the thiophosphoric acid/acrylate ratio: 2/1.[14]

After the reaction, the excess of thiophosphoric acid was washed off with a basic solution (NaOH, 1M) and the thiolophosphates were obtained in 89–97% yields (no other product was detected by ^{1}H and ^{31}P NMR).[15] The aqueous solution could be acidified with HCl 4 M until pH 1 to regenerate thiophosphoric acid for further reactions.

In conclusion, the Michael reaction with two equivalents of thiophosphoric acid for one equivalent of acrylate led quantitatively to β-carboxylated thiolophosphates in 1 h at 90°C and the excess of thiophosphoric acid could be reused. This reaction is unusual because acidic conditions are required unlike the traditional Michael reaction which was performed in a protic solvent with a catalytic or equimolar amount of base. Furthermore, this reaction without solvent could be of use as far as industry and the environment are concerned. It also complements previous methods for the synthesis of thiolophosphates.[16] Further studies of this efficient reaction are in progress, especially for *O*,*O*′-diarylphosphoric acids and methacrylate derivatives.



2a **6** **7**

Scheme 2. Secondary products of route a.

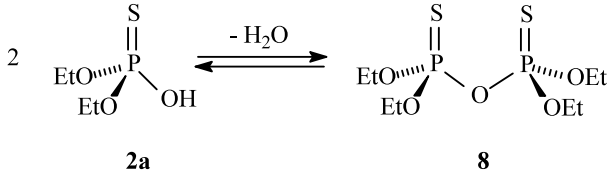
Table 2. Reaction between **2a** and Michael reagents

Entry	Michael reagent	Route	Time (h)	Isolated yields (%)	δ ^{31}P NMR (ppm)
1	CH_2=CH-COOH	b	24	96	27.5
2	CH_2=CH-CHO	b	12	95	26.7
3	CH_2=CH-CN	b	24	80	25.5
4	CH_2=CH-$CONH_2$	b	4	94	27.6
5	CH_2=CH-$CON(C_2H_5)_2$	a	10	95	27.8

Table 3. Reaction between TPA and acrylates at 90°C (80°C for methyl acrylate)

Entry	Product	R	R′	[TPA]	[A]	Time (h)	Conv. (%)	Isolated yield (%)	δ ^{31}P NMR (ppm)
1	**4a**	C_2H_5	CH_3	1	3	12	75		26.7
2	**4a**	C_2H_5	CH_3	1	2	12	73		26.7
3	**4a**	C_2H_5	CH_3	1	1	1	50		26.7
4	**4a**	C_2H_5	CH_3	1.1	1	1	45		26.7
5	**4a**	C_2H_5	CH_3	1.1	1	12	75		26.7
6	**4a**	C_2H_5	CH_3	1.5	1	1	55		26.7
7	**4a**	C_2H_5	CH_3	1.5	1	12	90		26.7
8	**4a**	C_2H_5	CH_3	2	1	1	>99	96	26.7
9	**4b**	C_2H_5	C_2H_5	2	1	1	>99	95	26.8
10	**4c**	C_2H_5	C_6H_5	1	3	12	72		26.7
11	**4c**	C_2H_5	C_6H_5	1	2	12	65		26.7
12	**4c**	C_2H_5	C_6H_5	1	1	1	55		26.7
13	**4c**	C_2H_5	C_6H_5	1.5	1	1	60		26.7
14	**4c**	C_2H_5	C_6H_5	1.5	1	12	93		26.7
15	**4c**	C_2H_5	C_6H_5	2	1	1	>99	97	26.7
16	**4d**	C_2H_5	$CH_2CH_2OC_2H_5$	2	1	1	98	89	26.7
17	**4e**	C_2H_5	$CH_2CH_2CH_2SC_2H_5$	2	1	1	98	92	29.3
18	**4f**	*i*-Pr	CH_3	2	1	1	>99	96	24.5
19	**4g**	*i*-Pr	C_2H_5	2	1	1	98	95	24.3
20	**4h**	*i*-Pr	C_6H_5	2	1	1	>99	96	25.3
21	**4i**	*i*-Pr	$CH_2CH_2OC_2H_5$	2	1	1	98	91	24.4
22	**4j**	*i*-Pr	$CH_2CH_2CH_2SC_2H_5$	2	1	1	98	93	24.2
23	**4l**	C_2H_5	$CH_2CH_2OC_6H_5$	2	1	1	>99	97	26.7
24	**4m**	*i*-Pr	$CH_2CH_2OC_6H_5$	2	1	1	>99	96	24.3

[TPA]: equivalent ratio of thiophosphoric acid.
[A]: equivalent ratio of acrylate.



2a **8**

Scheme 3. Dehydration of *O*,*O*′-diethyl thiophosphoric acid.

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14. Preparation of **4b** is a representative procedure for the synthesis of β-carboxylated thiophosphate: a mixture of 20 mmol of *O*,*O*′-diethylthiophosphoric acid, 10 mmol of ethyl acrylate and 0.1 mmol of MEHQ was stirred at 90°C for 1 h. The reaction mixture was allowed to cool down to room temperature and 50 mL of chloroform was added. The excess of thiophosphoric acid was washed off with a basic solution (3×10 mL NaOH, 1 M). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to yield a yellow colorless oil: 95%. ^{1}H NMR ($CDCl_3$/TMS 250 MHz): 4.25 (4H, m), 4.10 (2H, q, $J=6.9$ Hz), 3.05 (2H, m), 2.72 (2H, t, $J=7.1$ Hz), 1.31 (6H, m), 1.22 (3H, t, $J=6.9$ Hz) ppm; ^{13}C NMR ($CDCl_3$/TMS): 170.6, 60.5 (2C, d, $J=6.4$ Hz), 60.2, 35.2 (d, $J=3.9$ Hz), 25.3 (d, $J=4.1$ Hz), 15.6 (2C, d, $J=7.4$ Hz), 13.8 ppm; ^{31}P NMR ($CDCl_3$/H_3PO_4-85%): 26.7 ppm; FT-IR ($CHCl_3$): 1740 (C=O), 1260 (P=O), 1160 (P-OEt) cm^{-1}.
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