A New One-Pot Synthesis of Dialkyl Phosphonates from Diazo Compounds and Dialkyl Hydrogen Phosphites

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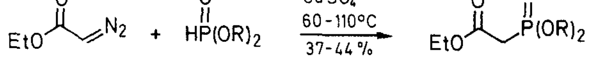
Bis(acetylacetonato)copper(II) is an effective catalyst for the preparation of dialkyl phosphonates from diazo compounds and dialkyl hydrogen phosphites. This method complements the classical ones and makes 2-dialkoxyphosphoryl-1,3-dicarbonyl compounds available.

The interest in dialkyl phosphonates is caused by their ability (in organic solution) to extract heavy-metal salts from aqueous solutions,[1] by their use as pesticides,[2] and by their use in the synthesis of olefins.[3] In addition to the classical synthesis of phosphonic esters by the Arbuzov and Michaelis–Becker reactions, several new routes to these esters have been reported.[4–6] Nevertheless, the synthetic routes to dialkyl phosphonates are rather limited by the availability of the starting compounds and by possible undesired side reactions, in particular, in the preparation of dialkyl 1-acyl-2-oxoalkylphosphonates (2-dialkoxyphosphoryl-1,3-dicarbonyl compounds).

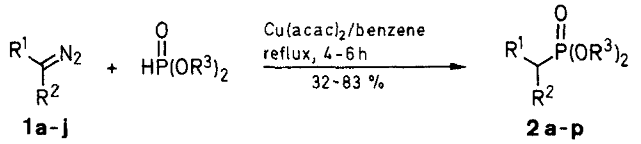
The reaction of alkyldiazoacetates with dialkyl hydrogen phosphites in the presence of copper(II) sulfate as a heterogeneous catalyst[7,8] affords only the relatively simple dialkyl dialkoxyphosphorylacetates in moderate yields.



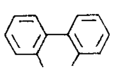
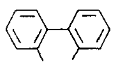
In a previous paper, we reported the novel preparation of 2-dialkoxyphosphoryl-1,3-diketones from 2-diazo-1,3-diketones and dialkyl hydrogen phosphites in the presence of copper(II) sulfate.[9] This method required an excess of the phosphite component and heating of the reaction mixture at a high temperature, without solvent. We now report the use of a homogeneous catalyst, bis(acetylacetonato)copper(II) [$Cu(acac)_2$], in the analogous reaction of a variety of diazo compounds **1** with dialkyl hydrogen phosphites to give a wide range of dialkyl phosphonates **2**. The reaction proceeds via carbenoid insertion into the P–H bond of the phosphite.

The above method gives a twofold increase in yields with ethyl diazoacetate (**1f**) and purer products in the case of 2-diazo-1,3-dicarbonyl compounds **1g–j** (Table 1). As compared to other syntheses of dialkyl phosphonates, the above method affords higher yields or it hitherto is the only method for the preparation of dialkyl phosphonates **2e–h, n, o, p**.

The optimum molecular ratio diazo compound/catalyst was studied for the reactions of diphenyldiazomethane (**1a**), diazofluorene (**1b**), and methyl-2-diazo-3-oxobutanoate (**1h**) with dimethyl hydrogen phosphite (Table 2). It was found to be 23:1 for preparation of products **2b,c,e** and 33:1 for that of the other products **2**.



1a-j **2a-p**

1	2	R¹	R²	R³
a	**a**	Ph	Ph	Me
a	**b**	Ph	Ph	Et
a	**c**	Ph	Ph	*i*-Pr
b	**d**			Me
b	**e**			Et
c	**f**	Ph	COPh	Me
c	**g**	Ph	COPh	Et
d	**h**	Ph	COMe	Me
d	**i**	Ph	COMe	Et
e	**j**	Ph	CO_2Et	Me
e	**k**	Ph	CO_2Et	Et
f	**l**	H	CO_2Et	Et
g	**m**	CO_2Me	CO_2Me	Me
h	**n**	CO_2Me	COMe	Me
i	**o**	COMe	COMe	Me
j	**p**	COPh	COPh	Me

The optimum molecular ratio dialkyl hydrogen phosphite/diazo compound is 5:1. Use of an only 1.5:1 ratio in the reaction of diazoester **1h** with dimethyl hydrogen phosphite leads to a decrease in yield of **2n** from 47% to 23%, whereas use of the high ratio 15:1 leads to a decrease in yield to 36%. If the diazo compound **1h** and the phosphite are added too rapidly or all at once to the catalyst (cf. procedure) the yield of **2n** is also lowered to 35%. The use of bis(hexafluoroacetylacetonato) copper(II) [$Cu(HFacac)_2$] in the reactions of **1a** and **1h** with dimethyl hydrogen phosphite using a 30:1 ratio diazo compound/catalyst results in decrease of the yields to 30% and 27%, respectively.

Electron-withdrawing substituents on acetylacetone ligands in copper(II)complexes have been shown to favor the association of further ligands onto the copper atom.[10,11] Presumably, the dialkyl hydrogen phosphite can convert the catalyst into a complex in which dialkyl hydrogen phosphite is strongly bonded to copper(II). The degree of dissociation of this complex controls the content of catalytic particles and thereby the yield of products. This assumption is proven by the decrease in yield when a higher ratio phosphite/**1h** is used and by IR-spectrometric evidence of complex formation of $Cu(acac)_2$ and $Cu(HFacac)_2$ with dimethyl hydrogen phosphite in boiling benzene.

We have already shown the applicability of the above method to the synthesis of dialkyl thiophosphonates.[12]

In summary the synthesis of dialkyl phosphonates from diazo compounds and dialkyl hydrogen phosphites under

Table 1. Dialkyl Phosphonates **2** Prepared

Product	Yield[b] (%)	mp (°C) or bp (°C)/Torr	R_f[c]	$^{20}n_D$	Molecular Formula[d] or Lit. Data	^{1}H-NMR (CCl_4/$HMDSO_{int}$)[e] δ, J(Hz)	^{31}P-NMR (CH_2Cl_2/H_3PO_{4ext})[f] δ
2a	52	95–96 (cyclohexane)	0.33		95–96[13]	3.38 (d, 6H, $J = 10$), 4.25 (d, 1H, $J = 22$), 6.95–7.45 (m, 10H)	25
2b	59	27–28.5 (cyclohexane)	0.45		22–25[14]	0.99 (m, 6H, $J = 7$), 3.45–3.99 (m, 4H), 4.25 (d, 1H, $J = 24$), 6.89–7.49 (m, 10H)	22
2c	64	80–81 (cyclohexane)	0.54		83–84[15]	0.82 (d, 6H, $J = 6$), 1.2 (d, 6H, $J = 6$), 4.14 (d, 1H, $J = 22$), 4.35 (m, 1H), 6.95–7.47 (m, 10H)	20
2d	56	102–104 (cyclohexane)	0.25		109–110[13]	3.37 (d, 6H, $J = 10.8$), 4.39 (d, 1H, $J = 30$), 7.05–7.73 (m, 8H)	26
2e	77	oil	0.33	1.5760	$C_{17}H_{19}O_3P$ (302.2)	0.97 (m, 6H, $J = 8$), 3.49–3.95 (m, 4H), 4.27 (d, 1H, $J = 30$), 6.99–7.63 (m, 8H)	21
2f	76	139.5–140.5 (BuOH)	0.26		$C_{16}H_{17}O_4P$ (304.3)	3.69 (d, 3H, $J = 11$), 3.76 (d, 3H, $J = 11$), 5.29 (d, 1H, $J = 21.5$), 7.06–7.89 (m, 10H)[g]	24
2g	76	oil	0.27	1.6343	184/0.5[16]	1.2 (m, 6H, $J = 7$), 3.65–4.29 (m, 4H), 5.4 (d, 1H, $J = 22$), 6.95–7.99 (m, 10H)	21
2h	42	150–170/0.05	0.17	1.5138	$C_{11}H_{15}O_4P$ (242.3)	2.22 (s, 3H), 3.55 (d, 3H, $J = 11$), 3.62 (d, 3H, $J = 11$), 4.48 (d, 1H, $J = 23$), 7.02–7.45 (m, 5H)	18
2i	41	oil	0.24		118–123/0.05[4]	1.12 (m, 3H, $J = 6.4$), 1.22 (m, 3H, $J = 6.4$), 2.20 (s, 3H), 3.59–4.47 (m, 5H), 6.95–7.30 (m, 5H)	16
2j	40	145–155/0.05	0.22	1.5225	$C_{12}H_{17}O_5P$ (272.2)	1.15 (m, 3H, $J = 5.7$), 3.48 (d, 3H, $J = 11.4$), 3.54 (d, 3H, $J = 11.4$), 4.00 (k, 4H, $J = 5.7$), 4.07 (d, 1H, $J = 22.8$), 6.95–7.35 (m, 5H)	20
2k	32	oil	0.36	1.4921	180–181/3[17]	0.96–1.42 (m, 9H), 3.56–4.22 (m, 7H), 6.99–7.4 (m, 5H)	19
2l	83	84–85/0.05	0.23	1.4330	142–145/9[8]	1.32 (m, 3H, $J = 7$), 1.37 (m, 6H, $J = 6$), 2.87 (d, 2H, $J = 23$), 3.84–4.31 (m, 6H)	18
2m	52	83–85/0.02	0.18	1.4400	130–131/10[18]	3.76 (s, 6H), 3.79 (d, 6H, $J = 11.5$), 4.14 (d, 1H, $J = 22$)	24
2n	47	82–83/0.09	0.27	1.4646	103/2[18]	2.34 (s, 0.21H), 2.44 (d, 2.3H, $J = 0.8$), 2.49 (d, 0.5H, $J = 1.1$), 2.86 (d, 0.07H, $J = 21$), 3.64 (d, 1H, $J = 12$), 3.67 (s, 2.3H), 3.69 (s, 0.5H), 3.71 (d, 4.6H, $J = 12$), 3.72 (s, 0.21H), 3.79 (d, 0.42H, $J = 12$), 13.77 (s, 0.77H), 14.6 (s, 0.17H)	14, 20, 26[h]
2o	50	70–71/0.09	0.15	1.4758	66–67/0.07[9]	2.44 (s, 6H), 3.73 (d, 6H, $J = 11$), 18.5 (s, 1H)	22
2p	36	144–145 (pet.ether/ benzene, 1 : 1)			144–145[9]	3.74 (d, 1.44H, $J = 12$), 3.82 (d, 4.56H, $J = 12$), 6.26 (d, 0,24H, $J = 22$), 6.90–8.10 (m, 10H)	18, 26[h]

[a] The IR spectra were in good accord with the proposed structures.

[b] Yield of isolated product, based on **1**. Molecular ratio diazo compound **1**/Cu(acac)$_2$ = 23 : 1 in the synthesis of **2b,c,e**, and 33 : 1 in all other cases.

[c] On plates Silufol-254 UV with EtOAc as eluent.

[d] Satisfactory microanalyses: C ±0.43, H ±0.13, P ±0.31.

[e] Recorded on a Varian-HA 100 MHz instrument. HMDSO = hexamethyldisiloxane.

[f] Recorded on an 8 MHz spectrometer.

[g] Recorded in $CDCl_3$.

[h] Mixture of tautomers.

homogeneous catalysis by Cu(acac)$_2$ complements the existing methods, in particular in the synthesis of 2-dialkoxyphosphoryl-1,3-dicarbonyl compounds.

All operations are carried out under an argon atmosphere. Benzene was distilled from sodium benzophenone ketyl. Diazo compounds **1a–j** were prepared according to known procedures.[19]

Dialkyl Phosphonates 2a–l; General Procedure:

A solution of the diazo compound **1a–e** (5.2 mmol) in benzene (15 mL) is added dropwise, over 3 h, to a stirred boiling solution of Cu(acac)$_2$ (42 mg, 0.16 mmol) and a dialkyl hydrogen phosphite

Table 2. Effect of the Molecular Ratio Diazo Compound **1**/Catalyst on the Yield of Dialkyl Phosphonates **2**

Diazo Compound	Yield (%)						
	Molecular Ratio **1**/Cu(acac)$_2$						
	5	10	23	32	42	75	200
1a	27	40	49	52	44	26	
1b			38	56			
1h		42	45	47	43		33

(26 mmol) in benzene (15 mL) and stirring and heating are continued for 1 h. The mixture is then cooled to r.t. and chromatographed on silica gel (column 15 × 1.7 cm) using benzene (150 mL) as eluent to give products **2a–e,g–l**. In the preparation of **2f**, the mixture is instead evaporated under reduced pressure, then cooled, and product **2f** is isolated by suction and recrystallized from BuOH.

Dialkyl Phosphonates 2m–p; General Procedure:
A solution of the diazo compound **1f–j** (14 mmol) and $HP(O)(OMe)_2$ (7.26 g, 66 mmol) in benzene (20 mL) is added dropwise, over 3 h, to a stirred boiling solution of $Cu(acac)_2$ (116 mg, 0.44 mmol) and $HP(O)(OMe)_2$ (440 mg, 4 mmol). Stirring and heating are continued for 3 h. The solvent is then evaporated, excess $HP(O)(OMe)_2$ is removed under reduced pressure, and the crude product **2m,n,o** is purified by distillation; product **2p** is isolated by filtration of the concentrated reaction mixture and recrystallized from petroleum ether/benzene.

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