

Preparation and Reactivity of β -Zinc and Copper Phosphonates

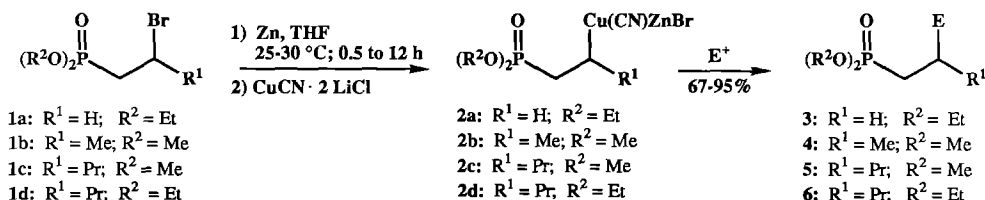
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Summary: Several zinc and copper β -metallated alkylphosphonates of type 2 have been prepared by the insertion of zinc to dialkyl β -bromoalkylphosphonates of type 1. This new class of d^2 reagents reacts in excellent yields with a broad range of electrophiles such as acyl chlorides, aldehydes, enones, acetylenic esters, allylic and alkynyl halides, trialkyltin halides and nitro olefins.

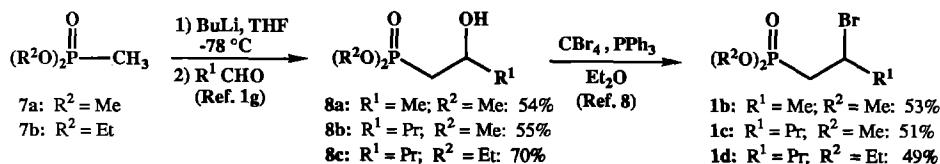
α -Metallated phosphonates are versatile d^1 reagents¹ which have found numerous applications in organic syntheses.^{2,3} They can be readily prepared by the α -lithiation of phosphonates² or by the addition of organocopper derivatives to α , β -unsaturated phosphonates.³ β -Metallated phosphonates cannot be obtained by these methods and we report herein a zinc-mediated approach to this new class of reagents.¹ Thus, the treatment of the α , β -bromophosphonate **1a**⁴ with zinc dust⁵ in THF at 30 °C for 12 h affords the corresponding alkylzinc bromide in 90% yield.⁶ The addition of the soluble copper salt CuCN·2 LiCl (1 eq.) at 0 °C transmetallates the intermediate zinc compound to the copper compound **2a**. Substituted derivatives of **1a** such as **1b-1d** can be prepared in two steps from dimethyl or diethyl methanephosphonate **7a-b** in 30-35% overall yields (see Scheme II). These secondary bromides insert zinc even more rapidly (25 °C, 30 min.) and remarkably, the β -functionalized organometallics formed show no tendency to eliminate BrZnP(O)(OR)₂.⁷

Scheme I



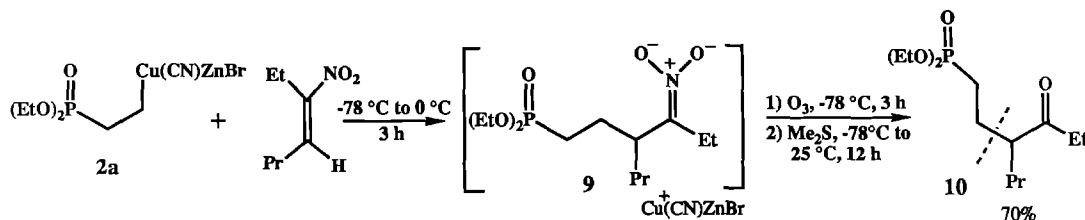
The copper-zinc reagents **2a-2d** were found to react with various electrophiles in high yields (67-95%; see scheme I and Table I). Their reaction with trialkyltin chlorides affords β -trialkylstannylphosphonates (25 °C, 1 h); see entries 1 and 19. Attempts to transmetallate the tin derivative **3a** to the corresponding β -lithiated phosphonate with butyllithium did not succeed. Aldehydes⁹ react in the presence of 2 equiv. of BF₃·OEt₂ (-78 °C to -15 °C, overnight) to give γ -hydroxyphosphonates (see entries 2,3 and 18), whereas the reaction of organocoppers **2** with acyl chlorides¹⁰ furnishes γ -ketophosphonates (0 °C, 2-5 h); see entries 4-6. The 1,4-addition of the reagent **2a** to enones in the presence of chlorotrimethylsilane^{10,11} gives the desired 1,4-adduct in satisfactory yields (Me₃SiCl (2 eq.), -78 °C to 25 °C, overnight); see entries 7-8. 3-Iodo-2-cyclohexenone reacts in very high yields (-30 °C, overnight) with **2a** and **2c** affording the addition-elimination products **3i** and **5b** respectively; see entries 9 and 20. Functionalized allylic bromides such as ethyl α -(bromomethyl)acrylate¹² or 3-bromo-2-t-butylsulfonyl-1-propene¹³ undergo a selective monocoupling reaction with **2a** leading to the allylated phosphonates **3j** (92%) and **3k** (79%); see

Scheme II



entries 10 and 11. The Michael-addition of the reagent **2** to nitro olefins¹⁴ proceeds very efficiently (see entries 15, 16, 17 and 21) giving δ -nitrophosphonates.¹⁵ The addition of **2a** to 3-nitro-3-heptene followed by a Nef reaction¹⁶ (O_3 , $-78^\circ C$, 3h; then Me_2S , $-78^\circ C$ to $25^\circ C$, overnight) allows in a one-pot procedure, a direct conversion of the intermediate nitronate **9** to the ketone **10** in 70% overall yield; see Scheme III. Finally the addition to acetylenic mono and diesters was found to give stereospecifically¹⁷ the syn-adducts **3l** and **3m** in 85% and 91% yield respectively (see entries 12, 13). The coupling of **2a** with 1-bromooctyne¹⁸ furnishes the alkynylphosphonate **3n** in 89% yield (see entry 14).

Scheme III



The easy insertion of zinc to β -bromoalkylphosphonates allows a general approach to a new class of d^2 reagents¹. After a transmetalation to the corresponding copper derivatives, they react with a wide range of electrophiles leading to a variety of polyfunctional phosphonates. Extensions of this methodology are currently underway in our laboratories.

Typical procedure: The addition of the copper-zinc reagent **2c** to 3-iodo-2-cyclohexenone (entry 20 of Table I).

(a) Preparation of the zinc-copper reagent **2c**. A solution of 2.59 g (10 mmol) of dimethyl 2-bromopentanephosphonate **1c** in 10 mL of THF was slowly added at $25^\circ C$ to 1.96 g (30 mmol) of zinc dust⁵ previously activated with 200 mg of 1,2-dibromoethane and 0.1 mL of Me_3SiCl .¹⁰ The addition is exothermic and the temperature reaches $45^\circ C$. GLC analysis of a hydrolyzed reaction aliquot showed the complete consumption of the starting bromide and the formation of dimethyl pentanephosphonate. The zinc reagent solution was added to a solution of 0.72 g (8 mmol) of copper cyanide and 0.68 g (16 mmol) of lithium chloride in 8 mL of THF at $-40^\circ C$. The reaction mixture was then warmed up to $0^\circ C$ and was ready to use.

(b) Reaction with 3-iodo-2-cyclohexenone. The previously prepared solution of **2c** was cooled to $-78^\circ C$ and 1.33 g (6 mmol) of 3-iodo-2-cyclohexenone in 2 mL of THF was slowly added. The reaction mixture was warmed up to $-30^\circ C$ and stirred 4 h at this temperature. After the usual work-up using ethyl acetate as extraction solvent an oil was obtained containing the desired product **5b** and a substantial amount of dimethyl pentanephosphonate (which proved to be difficult to separate by chromatography). The residue was transferred to a short-path distillation apparatus and the dimethyl pentanephosphonate was separated by distillation (b.p. $52^\circ C$ at 0.03 mm Hg). The residue was then purified by flash chromatography (solvent $MeOH/CH_2Cl_2$: 5/95) to afford 1.56 g (95% yield) of the analytically pure ketophosphonate **5b** (see entry 20 of Table I).

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Table I. Preparation of the Polyfunctional Phosphonates 3-6 by the Reaction of the Copper-Zinc Reagents 2a-2d with Electrophiles

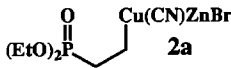
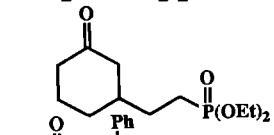
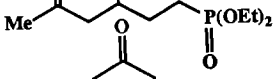
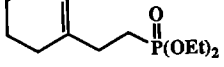
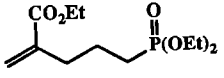
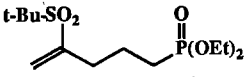
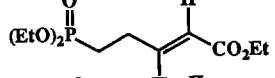
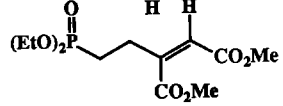
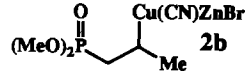
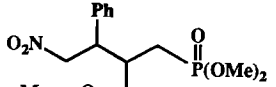
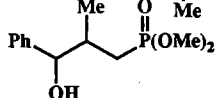
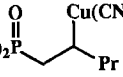
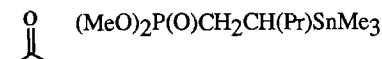
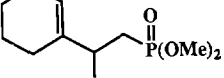
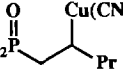
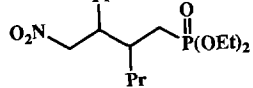
Entry	Copper-Zinc Reagent	Electrophile	Products of Type 3-6	Yield (%) ^a
1		Bu ₃ SnCl	(EtO) ₂ P(O)(CH ₂) ₂ SnBu ₃	3a 81
2	2a	PhCHO	(EtO) ₂ P(O)(CH ₂) ₂ CH(OH)Ph	3b 96
3	2a	HexCHO	(EtO) ₂ P(O)(CH ₂) ₂ CH(OH)Hex	3c 88
4	2a	PhCOCl	(EtO) ₂ P(O)(CH ₂) ₂ (CO)Ph	3d 96
5	2a	c-HexCOCl	(EtO) ₂ P(O)(CH ₂) ₂ (CO)c-Hex	3e 86
6	2a	PentCOCl	(EtO) ₂ P(O)(CH ₂) ₂ (CO)Pent	3f 84
7	2a	cyclohexenone		3g 71
8	2a	benzylidene acetone		3h 88
9	2a	3-iodo-2-cyclohexenone		3i 86
10	2a	ethyl α-(bromomethyl)acrylate		3j 92
11	2a	3-bromo-2-t-butylsulfonyl-1-propene		3k 79
12	2a	H≡CO ₂ Et		3l 85
13	2a	MeO ₂ C≡CO ₂ Me		3m 91
14	2a	Hex≡Br	(EtO) ₂ P(O)(CH ₂) ₂ ≡Hex	3n 89
15	2a	1-nitropentene	(EtO) ₂ P(O)(CH ₂) ₂ CH(Pr)CH ₂ NO ₂	3o 80
16	2a	β-nitrostyrene	(EtO) ₂ P(O)(CH ₂) ₂ CH(Ph)CH ₂ NO ₂	3p 81
17		β-nitrostyrene		4a 91 ^{b,c}
18	2b	PhCHO		4b 81 ^{b,d}

Table I. (Continued)

19		2c	Me ₃ SnCl		5a	67
20	2c	3-iodo-2-cyclohexenone		5b	95	
21		2d	1-nitropentene		6a	79b,e

^a All yields refer to isolated yields of analytical pure products (purity > 98%). Satisfactory spectral data (IR, ¹H and ¹³C NMR, mass spectra and high resolution mass spectra) were obtained for all compounds; ^b A mixture of two diastereoisomers is formed; ^c d.r. (diastereomeric ratio): 70:30; ^d d.r. = 64:36; ^e d.r. = 52:48.

References and Notes

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