

Preparation and Reactivity of β -Zinc and Copper Phosphonates

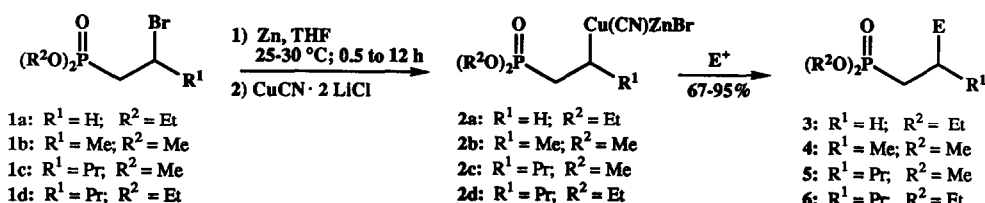
Carole Retherford, Tso-Sheng Chou, Robert M. Schelkun and Paul Knochel*

The Willard H. Dow Laboratories, Department of Chemistry, The University of Michigan
Ann Arbor, MI 48109

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.

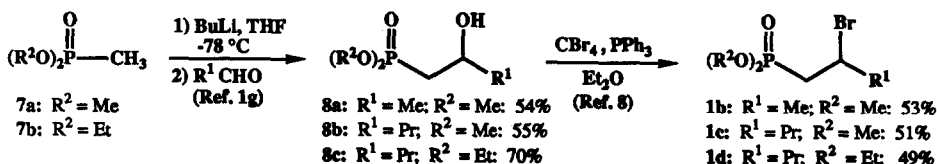
α -Metallated phosphonates are versatile d^1 reagents¹ which have found numerous applications in organic syntheses.^{2,3} They can be readily prepared by the α -lithiation of phosphonates² or by the addition of organocopper derivatives to α , β -unsaturated phosphonates.³ β -Metallated phosphonates cannot 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



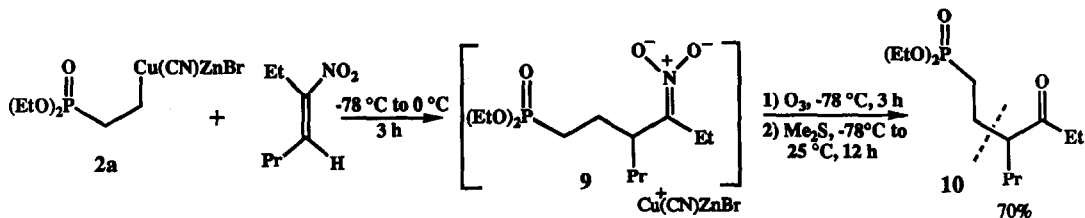
The copper-zinc reagents **2a-2d** were found to react with various electrophiles in high yields (67-95%; see scheme I and Table I). Their reaction with trialkyltin chlorides affords β -trialkylstannyphosphonates (25 °C, 1 h); see entries 1 and 19. Attempts to transmetallate the tin derivative **3a** to the corresponding β -lithiated phosphonate with butyllithium did not succeed. Aldehydes⁹ react in the presence of 2 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$ (-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 (Me_3SiCl (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 (O₃, -78°C, 3h; then Me₂S, -78°C to 25°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-bromoocetyne¹⁸ 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 transmetallation 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 °C to 1.96 g (30 mmol) of zinc dust⁵ previously activated with 200 mg of 1,2-dibromoethane and 0.1 mL of Me₃SiCl.¹⁰ The addition is exothermic and the temperature reaches 45 °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 °C. The reaction mixture was then warmed up to 0 °C and was ready to use.

(b) Reaction with 3-iodo-2-cyclohexenone. The previously prepared solution of 2c was cooled to -78 °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 °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 °C at 0.03 mm Hg). The residue was then purified by flash chromatography (solvent MeOH/CH₂Cl₂: 5/95) to afford 1.56 g (95% yield) of the analytically pure ketophosphonate 5b (see entry 20 of Table I).

Acknowledgments: We thank the National Institutes of Health (GM 41908) for the generous support of this work and Jennifer L. Gage and Gregory F. Nieckarz for some preliminary experiments.

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

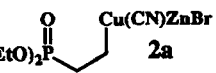
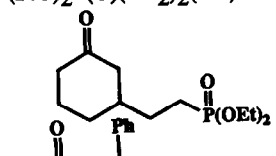
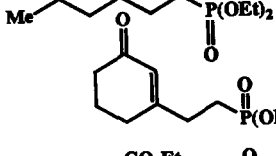
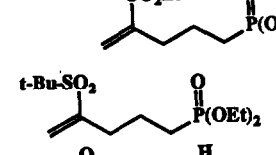
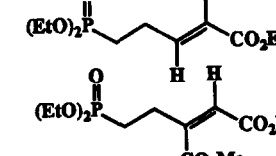
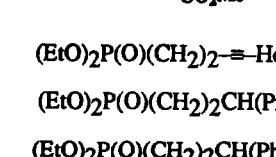
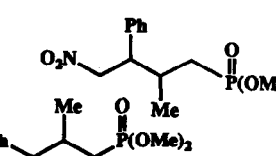

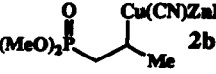
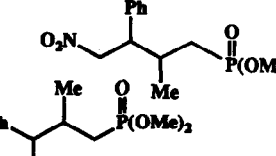

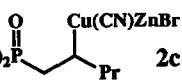
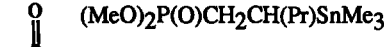
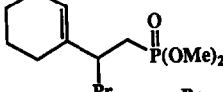
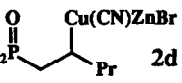
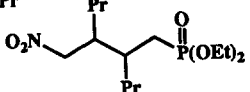
Entry	Copper-Zinc Reagent	Electrophile	Products of Type 3-6	Yield (%) ^a
1		Bu ₃ SnCl	(EtO) ₂ P(O)(CH ₂) ₂ SnBu ₃	3a 81
2	2a	PhCHO	(EtO) ₂ P(O)(CH ₂) ₂ CH(OH)Ph	3b 96
3	2a	HexCHO	(EtO) ₂ P(O)(CH ₂) ₂ CH(OH)Hex	3c 88
4	2a	PhCOCl	(EtO) ₂ P(O)(CH ₂) ₂ (CO)Ph	3d 96
5	2a	c-HexCOCl	(EtO) ₂ P(O)(CH ₂) ₂ (CO)c-Hex	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 91b,c
18	2b	PhCHO		4b 81b,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,c

^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

- Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
- (a) Corey, E.J.; Shulman, J.I. *J. Org. Chem.* **1970**, *35*, 777; (b) Kluge, A.F.; Cloudsdale, I.S. *J. Org. Chem.* **1979**, *44*, 4847; (c) Collard, J.-N.; Benezra, C. *Tetrahedron Lett.* **1982**, *23*, 3725; (d) Thangaraj, K.; Srinivasan, P.C.; Swaminathan, S. *Synthesis* **1982**, 855; (e) Kawashima, T.; Ishii, T.; Inamoto, N. *Chem. Lett.* **1983**, 1375; (f) Schaumann, E.; Fittkau, S. *Tetrahedron Lett.* **1984**, *25*, 2325; (g) Mikolajczyk, M.; Balczewski, P. *Synthesis* **1984**, 691; (h) Imamoto, T.; Sato, K.; Johnson, C.R. *Tetrahedron Lett.* **1985**, *26*, 783; (i) Teulade, M.P.; Savignac, P.; Aboujaoude, E.E.; Collignon, N. *J. Organomet. Chem.* **1985**, *287*, 145; (j) Aboujaoude, E.E.; Lietje, S.; Collignon, N.; Teulade, M.P.; Savignac, P. *Tetrahedron Lett.* **1985**, *26*, 4435; (k) Kay, M.K.; Aboujaoude, E.E.; Collignon, N.; Savignac, P. *Tetrahedron Lett.* **1987**, *28*, 1263; (l) Meijs, G.F.; Eichinger, P.C.H. *Tetrahedron Lett.* **1987**, *28*, 5559.
- (a) Bodalski, R.; Michalski, T.J.; Monkiewicz, J. *Phosphorous and Sulfur* **1980**, *9*, 121; (b) Schaumann, E.; Fittkau, S. *Synthesis* **1983**, 449.
- Ford-Moore, A.H.; Howarth Williams, J. *J. Chem. Soc.* **1947**, 1465.
- The zinc dust used was purchased from Aldrich (-325 mesh).
- The polar phosphonate group considerably accelerates the rate of formation of the zinc organometallic (non-functionalized alkyl bromides usually cannot be converted to the corresponding organozinc compounds in THF).
- We reported recently that β-cyano zinc and copper organometallics also do not eliminate the cyano group at temperature below 30 °C see: (a) Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395; (b) Majid, T.N.; Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069.
- Hooz, J.; Gilani, S.S.H. *Can. J. Chem.* **1968**, *46*, 86.
- Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* **1988**, *29*, 3887.
- (a) Posner, G.H.; Whitten, C.E. *Org. Synth.* **1975**, *55*, 122; (b) Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
- (a) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019; (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047; (c) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025; (d) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.
- (a) Ramarajan, K.; Ramalingam, K.; O'Donnell, D.J.; Berlin, K.D. *Org. Synth.* **1983**, *61*, 56; (b) Cassady, J.M.; Howie, G.A.; Robinson, J.M.; Stamos, I.K. *Org. Synth.* **1983**, *61*, 77.
- Auvray, P.; Knochel, P.; Normant, J.F. *Tetrahedron* **1988**, *44*, 4495, 4509, 6095.
- Retherford, C.; Yeh, M.C.P.; Schipor, I.; Chen, H.-G.; Knochel, P. *J. Org. Chem.* **1989**, *54*, 5200.
- The addition of 2b to β-nitrostyrene has to be performed at -20 °C. We observed the formation of 27% of dimethyl 4-phenyl-2-propyl-3-butenylphosphonate (substitution of the NO₂ group by a dimethyl pentylphosphonate group) during the reaction of 2c to β-nitrostyrene if this reaction is performed at 0 °C.
- (a) McMurry, J.E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259; (b) Thompson, W.J.; Buhr, C.A. *J. Org. Chem.* **1983**, *48*, 2769; (c) Barrett, A.G.M.; Graboski, G.G.; Russell, M.A. *J. Org. Chem.* **1986**, *51*, 1012.
- For a rationalization of this stereochemistry see: Krause, N. *Tetrahedron Lett.* **1989**, *30*, 5219.
- Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799.