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Palladium-catalyzed copper(I) salt-mediated arylation of a bis(dimethylamino)phosphonyl-stabilized carbanion

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Abstract

The synthesis of new arylmethylphosphonic acid tetramethyl diamides by a palladium-catalyzed cross-coupling reaction of a bis(dimethylamino)phosphonylmethylcopper(I) reagent with aryl iodides is described. © 2000 Elsevier Science Ltd. All rights reserved.

Esters and amides of arylmethylphosphonic acids are versatile reagents for organic synthesis. Arylation of phosphonyl-stabilized carbanions is a possible route to their preparation. To date only three reports have been published describing the Pd-catalyzed arylation of carbanions of phosphonates. All these communications deal with phosphonates containing an additional α-electron-withdrawing group.[1] Recently two examples of arylation of carbanions derived from $MeP(O)(OEt)_2$ have been carried out under irradiation, by an $S_{RN}1$ mechanism.[2] Here we report on a new, efficient synthesis of diamides of arylmethylphosphonic acids by Pd-catalyzed arylation of a bis(dimethylamino)phosphonylmethylcopper(I) reagent with aryl iodides.

We have found that the coupling reaction of the bis(dimethylamino)phosphonylmethylcopper(I) reagent[3] generated from the corresponding lithium compound and a stoichiometric amount of copper(I) iodide, proceeds readily with aryl iodides in the presence of 4 mol% $Pd(OAc)_2$ and 4 mol% 1,2-bis(diphenylphosphino)ethane (dppe) on refluxing in THF, to give arylmethylphosphonic acid tetramethyl diamides in a good yields (Scheme 1). This reaction tolerates a variety of functional groups in the aromatic ring. The results are summarized in Table 1 (entries 1, 4–12).[4,5] The use of 0.5 equiv. CuI instead of 1 equiv. decreases the yields of the cross-coupling products.

In the case of dialkylphosphonylmethylcopper(I) compounds (Z=OEt, O*i*-Pr) the yields of the corresponding dialkyl arylmethylphosphonates are low (50–53% in the reaction with PhI). This can be explained by the reduced thermal stability of $(RO)_2P(O)CH_2Cu$ in comparison with $(Me_2N)_2P(O)CH_2Cu$.

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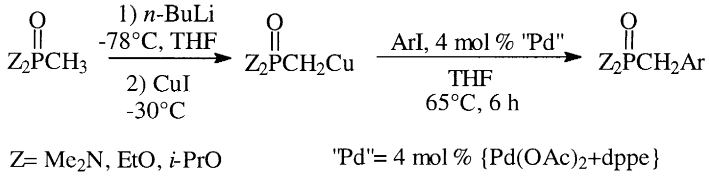


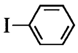
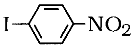
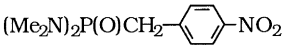
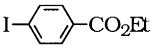
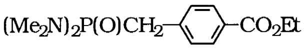
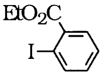
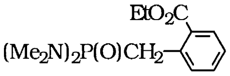
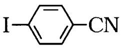
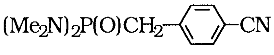
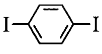
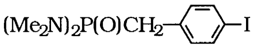
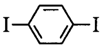
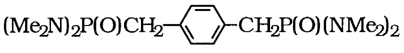
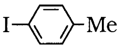
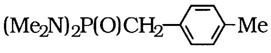
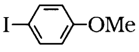
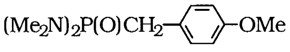
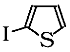
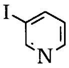
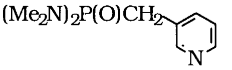
$$Z_2\overset{O}{\overset{\|}{P}}CH_3 \xrightarrow[\text{2) CuI, -30°C}]{\text{1) }n\text{-BuLi, -78°C, THF}} Z_2\overset{O}{\overset{\|}{P}}CH_2Cu \xrightarrow[\text{THF, 65°C, 6 h}]{\text{ArI, 4 mol\% "Pd"}} Z_2\overset{O}{\overset{\|}{P}}CH_2Ar$$

Z= Me_2N, EtO, *i*-PrO "Pd"= 4 mol% {$Pd(OAc)_2$+dppe}

Scheme 1.

Table 1

Cross-coupling of $(Me_2N)_2P(O)CH_2Cu$ with ArI (4 mol% $Pd(OAc)_2$/dppe; THF, 65°C, 6 h)

Entry	ArI	Product	mp, °C or n_D^{20}	Yield(%)	
				according to NMR ^{31}P spectrum	isolated yield
1			81	85	76
2[a]			141	77	70
3			114	86	75
4			1.5195	84	74
5			149	84	75
6			154	80	71
7[b]			201	48	35
8			112	74	63
9			85	72	62
10			75	79	69
11[c]			76	59	50

[a] 6 h, 20°C. [b] 3 equiv. $(Me_2N)P(O)CH_2Cu$, 8 mol% "Pd", 9h, 65°C. [c] Solvent THF/DMF

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2. Wong, J.-W.; Natalie Jr., K. J.; Nwokogu G. C.; Pisipati, J. S.; Flaherty, P. T.; Greenwood, T. D.; Wolfe, J. F. *J. Org. Chem.* **1997**, *62*, 6152–6159.
3. Mathey, F.; Savignac, Ph. *Tetrahedron* **1978**, *34*, 649–654.

4. The products were isolated by column chromatography (silica gel, ethyl acetate/methanol=5–10/1, Table 1 entries 1, 2, 4, 6, 7, 9, 11) or by recrystallization from heptane (entries 3, 5, 8) or hexane (entry 10). All new compounds have been fully characterized.
5. Typical experimental procedure: *n*-BuLi (2.82 ml of 1.86 M solution in hexane, 5.25 mmol) was placed in a flask equipped with a stirrer, an addition funnel and argon inlet tube. THF (3.3 ml) was added at −30°C, then methylphosphonic acid tetramethyldiamide (0.75 g, 5 mmol) in THF (2 ml) was added dropwise to the solution at −78°C for 15 min. After 15 min stirring at −78°C CuI (1 g, 5.25 mmol) was added. After 60 min at −30°C the mixture was allowed to warm up to 20°C. The resulting solution was added to a mixture, prepared by stirring ethyl 4-iodobenzoate (1.38 g, 5 mmol), $Pd(OAc)_2$ (44 mg, 0.2 mmol) and dppe (80 mg, 0.2 mmol) in THF (2 ml) at 20°C for 40 min. The reaction mixture was heated at 65°C for 6 h, evaporated, treated with water (10 ml), neutralized with HCl and filtered. The solid residue was washed with chloroform (5×6 ml). Water layer was extracted with chloroform (5×6 ml). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was recrystallized from heptane to give 1.12 g (75%) of ethyl 4-[[bis(dimethylamino)phosphonyl]methyl]benzoate as a colorless solid. Mp 114°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3H) and 4.30 (q, 2H, OCH_2CH_3), 2.48 (d, 12H, J=9.6 Hz, CH_3N), 3.20 (d, 2H, J=17.0 Hz, CH_2P), 7.33 (dd, 2H, J=8.2; 1.9 Hz, Ar), 7.92 (d, 2H, J=8.2 Hz, Ar). Anal. calcd for $C_{14}H_{23}N_2O_3P$: C, 56.37; H, 7.77; P, 10.38. Found: C, 56.70; H, 7.92; P, 10.48.