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A Facile and General Preparation of α,α-Difluoro Benzylic Phosphonates by the CuCl Promoted Coupling Reaction of the (Diethylphosphonyl)difluoromethylcadmium Reagent with Aryl Iodides

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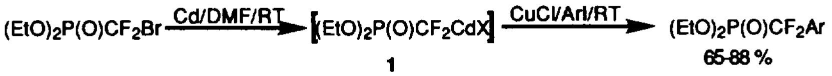
Abstract: *A series of α,α-difluorobenzylic phosphonates have been prepared in good yield (65-88%) by the CuCl promoted coupling reaction of the (diethylphosphonyl)difluoromethylcadmium reagent with aryl iodides.*

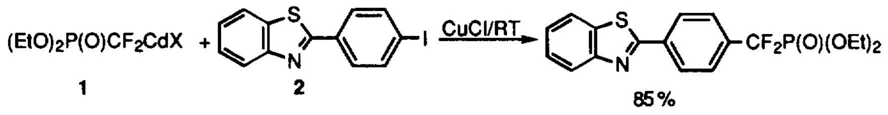
Recently, introduction of the difluoromethylenephosphonate moiety into organic molecules has attracted much attention due to the biological properties exhibited by these compounds as compared to their non-fluorinated phosphonate analogs.[1] It is known that some benzylic phosphonates are of important biological activity.[2] KB-944, for example, is an effective antihypertensive, vasodilator, antiarrythmic, and Ca antagonist.[3] The (diethylphosphonylmethyl)phenyl moiety has been incorporated into peptides for utilization as either product analog inhibitors of protein tyrosine kinases or as substrate analog inhibitors of protein tyrosine phosphonatases.[4] The preparations of α,α-difluoro alkylphosphonates have been well documented[5] and the biological activities of some α,α-difluoro alkylphosphonates have been discussed.[5i,6] However, there has been only one report describing the introduction of the difluoromethylene-phosphonate moiety into an aromatic ring, achieved by the reaction of benzylic α-oxophosphonates with 15 equivalents of DAST (as solvent) to form 43 - 79 % of α,α-difluoro benzylic phosphonates.[7] The lack of a general and convenient synthetic methodology for the preparation of α,α-difluoro benzylic phosphonates has delayed the investigation of this class of phosphonates. We now report a facile and general method for the preparation of α,α-difluoro benzylic phosphonates.

We have found that the coupling reaction of the (diethylphosphinyl)difluoromethylcadmium reagent 1, generated from diethyl bromodifluoromethylphosphonate and acid-washed cadmium powder, proceeds readily with aryl iodides in the presence of CuCl in DMF to give excellent yields of α,α-difluoro benzylic phosphonate at room temperature. The results are summarized in the Table.



$$(EtO)_2P(O)CF_2Br \xrightarrow{Cd/DMF/RT} \underset{\mathbf{1}}{[(EtO)_2P(O)CF_2CdX]} \xrightarrow{CuCl/ArI/RT} \underset{65\text{-}88\ \%}{(EtO)_2P(O)CF_2Ar}$$

A variety of functional groups, such as nitro, ether, ester, and halides, could be tolerated in the reaction. With halosubstituted aryl iodides (entries 4, 7, 9), the reaction selectively gave products coupled at the iodide. Upon reaction of excess cadmium reagent **1** with 1,4-diiodobenzene, the corresponding bisphosphonate was obtained (entry 8). No coupling product was isolated in the reaction of **1** with bromobenzene under similar conditions. DMF and triglyme were used as solvents for the coupling reaction. In the presence of CuCl, the (diethylphosphinyl)difluoromethylzinc reagent also coupled with aryl iodides to afford α,α-difluoro benzylic phosphonates. The coupling reaction required a stoichiometric amount of CuCl to achieve the best yields of the α,α-difluoro benzylic phosphonates. This method has been applied for the preparation of α,α-difluorinated KB 944. In the presence of CuCl, reaction of **1** with **2**[8] provided 85 % yield of α,α-difluorinated KB 944.

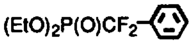
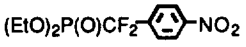
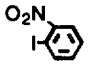
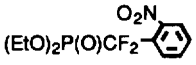
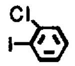
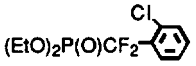
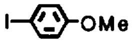
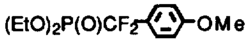
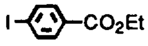
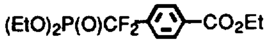
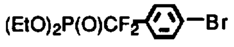


In a typical experiment, a flask fitted with a stir bar and a condenser topped with a nitrogen inlet was charged with 2.67 g (10.0 mmol) of diethyl bromodifluoromethylphosphonate, 1.25 g (11.0 mmol) of cadmium and 10 mL of dry DMF. The mixture was stirred at room temperature for 2 hours. The unreacted cadmium was removed by filtration under a nitrogen atmosphere and the filtrate was treated with 0.69 g (7.0 mmol) of CuCl and 1.50 g (6.0 mmol) of 4-nitroiodobenzene at room temperature for 3 hours. 100 mL of ether was added to the reaction mixture and the precipitated solids were removed by filtration and washed with 50 mL of ether. The combined ether solutions were washed with NH_4Cl (aq) and H_2O, dried over Na_2SO_4, and evaporated to give a residue, which was further purified by silica gel column chromatography with CH_2Cl_2/EtOAc (9:1) eluent to give 1.55 g (84 %) of diethyl α,α-difluoro-4-nitrobenzylphosphonate, mp 47-48°C. ^{19}F NMR ($CFCl_3$, $CDCl_3$) -110.1 (d, J = 110 Hz). ^1H NMR (TMS, $CDCl_3$) 1.35 (t, J = 7 Hz, 6H), 4.26 (m, 4H), 7.83 (d, J = 8 Hz, 2H), 8.33 (d, J = 8 Hz, 2H). ^{13}C NMR (TMS, $CDCl_3$) 16.4 (d, J = 6 Hz), 65.2 (d, J = 7 Hz), 117.3 (td, J = 264, 216 Hz), 123.6 (s), 139.0 (td, J = 22, 14

Hz), 149.5 (s), ^{31}P NMR (85 % H_3PO_4, $CDCl_3$) 5.3 (t, J = 110 Hz). GC-MS (m/e, rel. int.) 309 (M^+, 0.31), 263 (M^+-NO_2, 0.42), 172 (8.92), 137 (28.49), 109 (100). HRMS calcd for $C_{11}H_{14}F_2NO_5P$ [M^+] 309.0578. found. 309.0578. FTIR (CCl_4) 2986 (m), 2933 (w), 2914 (w), 1614 (w), 1533 (s), 1351 (s), 1275 (s), 1068 (s), 1047 (s), 1026 (vs), 856 (m) cm^{-1}.

Table: CuCl promoted coupling reaction of cadmium reagent 1 with aryl iodides

$$\underset{\mathbf{1}}{(EtO)_2P(O)CF_2CdX} \xrightarrow{CuCl/ArI/RT} (EtO)_2P(O)CF_2Ar$$

Entry	Aryl iodide	Product	Yield(%)[a]
1			80
2			84
3			83
4			88
5			85
6			84
7			70
8			75
9			65

a) Isolated yields. All products gave satisfactory ^{19}F, ^{1}H, ^{31}P, ^{13}C NMR, FT-IR and MS data.

The ready availability of precursors, mild reaction conditions, and excellent chemoselectivity make this approach a facile method for the synthesis of α,α-difluoro benzylic phosphonates.

Acknowledgment

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