New α-trifluoromethyl-substituted α-amino phosphonates

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The title α-amino phosphonates with orthogonal protective groups (Cbz/OMe, OEt) were obtained on addition of C-nucleophiles to highly electrophilic imines PG–N=C(CF_3)P(O)($OR)_2$.

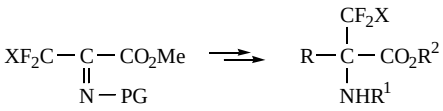
Table 1 Characteristics of compounds **2a**–**2g**.

Compound	R	R^1	mp/°C	Yield (%)
2a	Me	Me	—[a]	69
2b	Me	Bu^i	64–65	70
2c	Me	CH_2Ph	83–84	73
2d	Me	$CH_2CH{=}CH_2$	—[a]	71
2e	Et	$CH_2CH{=}CH_2$	—[a]	68
2f	Me	$CH_2CH_2CH{=}CH_2$	124–125	66
2g	Et	$CH_2CH_2CH{=}CH_2$	57–58	74

[a]Oil.

α-Amino phosphonates are important analogues of α-amino carboxylic acids, and their synthesis and biological activity have been a focus of attention in synthetic and medicinal chemistry.[1] These compounds can be potent antibacterial agents[2] and transition-state analogue inhibitors of proteolytic enzymes.[3]

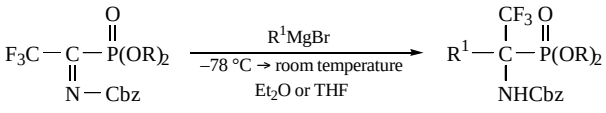
In the last decades, β-fluorinated α-amino acids have attracted a considerable interest as highly selective inhibitors of pyridoxal phosphate-dependent enzymes,[4] as well as candidates for the modification of biologically active peptides.[5] Recently,[6] we reported on a new effective pathway to α-halodifluoromethyl-substituted α-amino acids based on the amidoalkylation of carbon nucleophiles with highly electrophilic imines of methyl 3-halo-3,3-difluoropyruvates (Scheme 1).



X = F, Cl, Br, H

Scheme 1

We disclose an effective access to the phosphorous analogues of α-trifluoromethyl-substituted α-amino acids. We used new highly electrophilic α-CF_3 imino phosphonates[7] **1** with orthogonal protective groups (Cbz/OMe, OEt) as fluorine-containing



1 **2**

Cbz = C(O)OCH_2Ph

Scheme 2

building blocks. Despite the fact that some of these acyl imines were described,[8] they were not used for the preparation of α-amino phosphonates. Thus, we found that **1** smoothly reacted with organometallic reagents at –78 °C in THF or diethyl ether. The nucleophilic addition proceeds regiospecifically and results in alkylation of the C=N double bond to give corresponding α-amino phosphonates **2** in preparative yields (Scheme 2, Table 1).†

In summary, we obtained new orthogonally protected α-CF_3 α-amino phosphonates. Incorporation of these compounds into biologically active peptides is under current investigation.

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† *General procedure for the synthesis of α-amino phosphonates*: A Grignard reagent (solution in diethyl ether, 5.9 mmol) was added dropwise to a solution of 6 mmol of imine **1** in dry THF (25 ml) at –78 °C with stirring. After standing for 1 h at –78 °C, the reaction mixture was allowed to warm up to room temperature and stirred for 6 h. The reaction was quenched with a saturated NH_4Cl solution and extracted with diethyl ether (2×20 ml). The combined organic layer was washed with brine (25 ml), dried over $MgSO_4$ and filtered. The solvent was removed under a reduced pressure, and the crude product was purified by flash chromatography (ethyl acetate–light petroleum).

For **2a**: ^{1}H NMR ($CDCl_3$) δ: 7.33 (m, 5H, Ph), 5.43 (br. s, 1H, NH), 5.07 (s, 2H, OCH_2), 3.83 (d, 3H, OMe, $^3J_{P–H}$ 10.5 Hz), 3.81 (d, 3H, OMe, $^3J_{P–H}$ 10.5 Hz), 1.93 (d, 3H, Me, $^3J_{P–H}$ 16.0 Hz). ^{19}F NMR ($CDCl_3$) δ: –6 5.2 (d, 3F, CF_3, $^3J_{P–F}$ 5.0 Hz). ^{31}P NMR{^{1}H} ($CDCl_3$) δ: 20.4 (q, $^3J_{P–F}$ 5.0 Hz).

For **2b**: ^{1}H NMR ($CDCl_3$) δ: 7.35 (m, 5H, Ph), 5.33 (br. s, 1H, NH), 5.08 (m, 2H, OCH_2), 3.83 (d, 3H, OMe, $^3J_{P–H}$ 10.8 Hz), 3.81 (d, 3H, OMe, $^3J_{P–H}$ 10.8 Hz), 2.11 (m, 2H, CH_2), 2.05 (m, 1H, CH), 0.95 (m, 6H, 2Me). ^{19}F NMR ($CDCl_3$) δ: –6 0.5 (s, 3F, CF_3). ^{31}P NMR{^{1}H} ($CDCl_3$) δ: 20.2 (s).