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O-(DIPHENYLPHOSPHINYL)HYDROXYLAMINE: A NEW REAGENT FOR ELECTROPHILIC C-AMINATION

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Summary: O-(Diphenylphosphinyl)hydroxylamine efficiently aminates a variety of stabilised carbanions and certain Grignard reagents.

As part of a current project on the synthesis of nuclearly-modified cephems, we required a simple yet efficient route to the aminophosphonoacetate (1). The original, multi-step route[1] to this somewhat labile compound, a key building block in cephem total synthesis, involved acylation of the anion of the imine (2), followed by hydrolytic cleavage and chromatographic purification. Two shorter routes utilise the anion of the phosphonoacetate (3) (as the corresponding methyl or ethyl esters) and either O-mesitylenesulphonylhydroxylamine[2] (MSH) or trifluoromethanesulphonyl azide[3] as effective aminating agents. Neither proceeds in yields of greater than 50%, and the second is incompatible with the presence of the benzyl group of (1). Additionally, MSH is rather hazardous to handle on even a modest scale.[2,4]

$(EtO)_2P(O)CH(NH_2)CO_2CH_2Ph$

(1)

$(EtO)_2P(O)CH_2N{=}CHPh$

(2)

$(EtO)_2P(O)CH_2CO_2CH_2Ph$

(3)

$H_2N{-}OP(O)Ph_2$

(4)

Recently, the preparation and structure of O-(diphenylphosphinyl)hydroxylamine (4) have been discussed in detail.[5] With minor modifications, we find that this compound can be prepared in substantial amounts readily and directly from hydroxylamine hydrochloride, and can be stored indefinitely at -20°C. Further, we find that it acts as an excellent C-aminating agent towards a variety of stabilised carbanions and certain Grignard reagents.

Reaction of the sodium salt of the phosphonoacetate (3) with one equivalent of reagent (4) in THF at -78°C leads in one simple operation to the aminophosphonoacetate[6] (1), isolated as its stable crystalline hydrogen oxalate salt, in 60% yield. In a similar manner, reaction of the sodium salts of diethyl malonate and of malononitrile yielded diethyl aminomalonate (as the hydrogen oxalate salt) and aminomalononitrile (as the toluene-p-sulphonic acid salt) in 57% and 50% yields respectively. Use of the corresponding lithium salts of these species was considerably less effective, with yields of only 25-30% being attained.

Electrophilic amination of Grignard reagents is of considerable importance and current interest.[7] We find that, as representative examples, phenyl and hexyl magnesium bromide react with aminating agent (4) [2 moles Grignard: 1 mole (4), THF, -78°C] to give aniline and 1-aminohexane in 67% and 27% yields respectively, the yields being based on aminating agent. Use of phenyl lithium[8] produced only traces of aniline.

Further studies on the scope of this method for electrophilic *C*-amination are in progress.

O-(Diphenylphosphinyl)hydroxylamine: To a stirred aqueous solution of hydroxylamine hydrochloride (6.6M, 137 mmol) was added aqueous sodium hydroxide (7.1M, 116 mmol), followed by dioxan (66 ml). The resulting solution was cooled in an ice/salt bath, and freshly distilled diphenylphosphinyl chloride[5] (11.8 g, 50 mmol) in dioxan (50 ml) was added in one portion with vigorous stirring. Stirring was continued for 4 min as copious precipitation ensued. Water (200 ml) was added, and the slurry filtered. After drying *in vacuo* (P_2O_5, 3 hr), the crude product (9.9 g, 55% pure by iodometry[5]) was obtained. This material was purified by stirring as a slurry with aqueous sodium hydroxide (0.25M, 100 ml) at 0°C for 30 min, followed by filtration and drying as above. Such treatment afforded *O*-(diphenylphosphinyl)hydroxylamine (5.8 g, 90% pure by iodometry) of sufficient purity for normal use. It could be stored at -20°C for extended periods with no noticeable decomposition.

Benzyl α-Amino(diethylphosphono)acetate: Benzyl diethylphosphonoacetate[9] (1.14 g, 4 mmol) and sodium hydride (108 mg, 4.5 mmol) in THF (20 ml) were stirred for 1 hr at room temperature under Ar. The resulting solution was added dropwise, *via* a hypodermic syringe, to a stirred suspension of the aminating agent (1.02 g, 90% pure, 4 mmol) in THF (20 ml) at -78°C under Ar. The mixture was held at -78°C for a further 2 hr, then allowed to come to room temperature overnight. It was poured on to aqueous buffer (75 ml, pH8), solid NaCl added, then extracted with AcOEt (4 x 25 ml). The organic extracts were combined, dried, and concentrated. The resulting crude product was trituratively extracted with ether (25 ml), and this ethereal extract added slowly to a solution of anhydrous oxalic acid (720 mg, 8 mmol) in ether (10 ml). Filtration and washing of the solid with ether afforded the desired product in pure form as its hydrogen oxalate salt (910 mg, 60%), m.p. 122-123°C. This stable, non-hygroscopic salt could be stored indefinitely without precaution. Quantitative liberation of the free base was achieved by treatment with excess saturated aqueous K_2HPO_4 solution, and extraction of the amine into ether.

References and Notes.

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