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NOVEL PHOSPHORANE AND PHOSPHONATE SYNTHONS FOR VINYL GLYCINES

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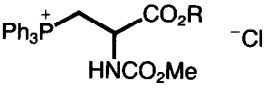
Summary: A versatile and convenient synthesis of 4-substituted vinyl glycines, employing novel phosphorane and phosphonate intermediates is reported.

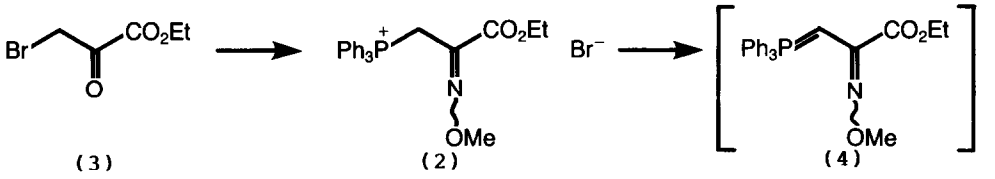
Recently there has been considerable interest in vinyl glycines as antibiotics[1], enzyme inhibitors[2] and synthetic intermediates. Although several syntheses of these compounds have been described[3], none provided the versatility that was required.

The phosphonium salt (1)[4], a glycine synthon derived from serine, is tedious to prepare and has to be used as its free acid to avoid β-elimination.

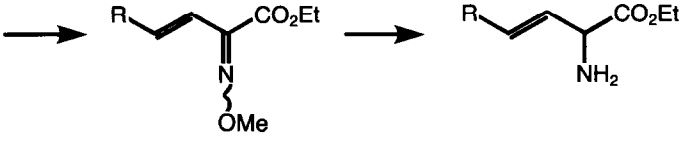


(1)

Therefore it was reasoned that the oxime (2) would provide advantages as an amino acid synthon. Crystalline (2)[5] was readily obtained from ethyl bromopyruvate (3) by treatment with methoxyamine hydrochloride in ethanol, followed by triphenylphosphine in refluxing THF.



(3) (2) (4)



(5) (6)

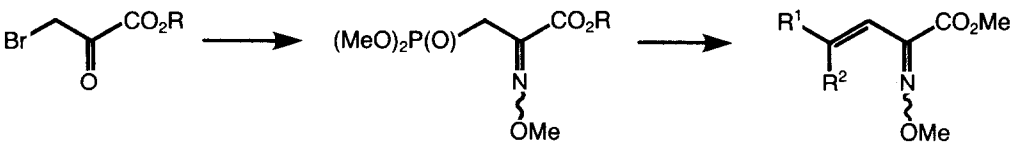
Conversion to the phosphorane (4) with base and reaction with aldehydes gave the required derivatives (5). Reactions with acetone and 1,1,1-trifluoroacetone failed. n-Butyl lithium was the initial base chosen for the generation of (4). Owing to the partially stabilised nature of this phosphorane, although it could not be isolated, it was reasoned that a weaker base would suffice. Indeed, an investigation of the reaction of (4), generated with a range of bases, with n- butanal, showed that other bases could be used (see Table 1).

Table 1

Base	Solvent	Yield (%)
nBuLi	THF-DMPU[6]	45
NaH	DMF	15
K-phthalimide	THF-DMPU	21
K-OtBu	THF-DMPU	28
K_2CO_3	DMF	53
NEt_3	CH_2Cl_2	29

The preferred choice was potassium carbonate in DMF, which requires no special precautions and has, in subsequent examples, provided excellent yields. The β-vinyl-α-methoximino esters (5) can then be reduced with zinc in formic acid, to give the amino esters (6). Entry F in Table 2 shows that on reduction of ethyl 2-methoximino-4-phenylbut-3(E)-enoate (5; R = Ph), the required product (6) (R = Ph) was obtained on work-up as an inseparable mixture with ethyl 2-amino-4-phenylbut-2-enoate. This problem was overcome by first hydrolysing the ester and then reducing the oxime. This method was also used for entry G in Table 2, providing the amino acid in 58% yield from (5).

To increase the versatility of this approach, reaction with ketones was required. Hence the phosphonate (7a) was prepared, by reaction of (3a) with methoxyamine hydrochloride followed by trimethylphosphite. However, it was soon found that the use of the methyl ester (7b)[7], obtained from methyl bromopyruvate (3b), was superior, thereby avoiding transesterification during the phosphonate reaction.



(3) a; R = Et
b; R = Me

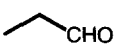
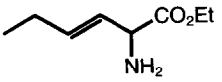
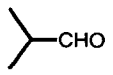
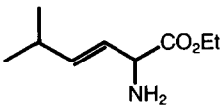
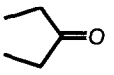
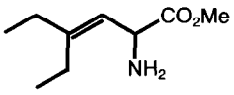
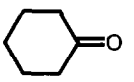
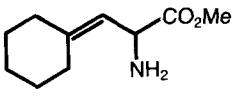
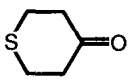
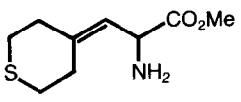
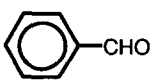
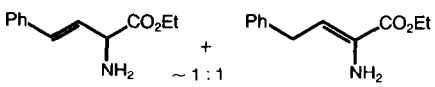
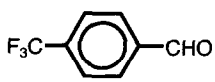
(7) a; R = Et
b; R = Me

(8)

The base of choice for the generation of the carbanion of (7b) was sodium hydride. n-Butyl lithium, sodium methoxide and sodium hydroxide-phase transfer catalyst gave inferior yields. It has also been shown that the phosphonate (7a) reacts with benzaldehyde to give (5) (R = Ph) in 31% yield (and 7% methyl ester), and that the product was identical with that obtained by reaction of the phosphorane (4) with benzaldehyde.

In conclusion, the phosphonium salt (2) and the phosphonate (7b) are readily available stable intermediates for the preparation of a wide range of 4-substituted vinyl glycines, with greater potential than has been exploited to date.

Table 2

Entry	Carbonyl Compound[a]	Yield of Oxime (%)	Protected Amino Acid	Yield (%)
A		50[b]		84
B		99[c]		94
C		24		99
D		36		49
E		54		37
F		77[b] 98[c]		65
G		99[c]	———	—

a: all ketones were reacted with (7b), all aldehydes with (4).
b: using nBuLi, THF, DMPU to generate (4).
c: using K_2CO_3, DMF to generate (4).

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5. Data: m.p. 137-139°C; found C, 59.56; H, 4.88; N, 2.82; Br, 16.54; P, 6.40%, $C_{24}H_{25}NO_3BrP$ requires C, 59.27; H, 5.18; N, 2.88; Br, 16.43; P, 6.37%; ν_{max} (KBr) 1715, 1434, 1108, 1040, 742, 691 and 510 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.15 (3H, t, J 7.1Hz), 3.80 (3H, s), 4.12 (2H, q, J 7.1Hz), 5.25 (2H, d, J 16.3Hz) and 7.66-7.90 (15H, m).

6. DMPU (N,N'-Dimethylpropyleneurea) is 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

7. Data: b.p. 159-161°C; found MH^+ 240.0638, $C_7H_{15}NO_6P$ requires 240.0637; ν_{max} (film) 1720, 1270, 1210, 1170, 1040, 850 and 780 cm^{-1}; δ_H (250MHz, $CDCl_3$) 3.34 (2H, d, J 23.5Hz), 3.75 (6H, d, J 11.2Hz), 3.89 (3H, s) and 4.13 (3H, s).

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