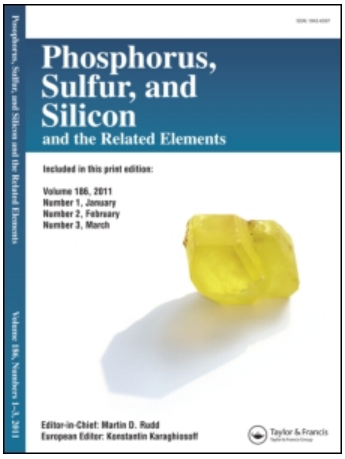

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SYNTHESIS OF γ-AMINOPROPYLPHOSPHONOUS ACIDS USING HYPOPHOSPHOROUS ACID SYNTHONS

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Abstract γ-Aminopropylphosphonous acids have been synthesised using hypophosphorous acid synthons

Work in these laboratories[1] has shown that phosphonous analogues of α-amino acids are excellent bio-isosteres, and act as false substrates that interfere with key metabolic pathways. We were therefore encouraged to examine further the phosphonous for carboxyl bio-isosteric replacement principle in the γ-amino carboxylic acid series; a series where much effort has already been devoted to the synthesis of GABA analogues, including phosphonic and phosphinic analogues, as possible therapeutic agents for central nervous system disorders.

At the outset of this work a patent describing the radical addition of sodium hypophosphite to allylamine was the only report of a phosphonous analogue of GABA[2]. However, this method has severe limitations for the synthesis of a range of substituted γ-aminophosphonous acids. The methods used for the synthesis of the phosphonic and methyl phosphinic analogues of GABA[3] were not directly applicable to the synthesis of the phosphonous analogues due to problems associated with the P-H bond. We have now overcome these problems by the use of synthons with the P-H bond protected.

The reaction of hypophosphorous acid with triethylorthoformate to give the phosphonite $(EtO)_2CHP(O)(OEt)H$ (1) has been reported by Gallagher et al.[4] and used by his group in the preparation of phospha-sugars[5]. Changes to the catalyst and reaction conditions have given us (1) in improved yield and quality.

We have found that (1) can function as a hypophosphorous acid synthon.

By refluxing (1) in HMDS, a good yield of the PIII silyl ester (2) is obtained. This new and reactive species is also a valuable hypophosphorous acid synthon.

$$(EtO)_2CHP(O)(OEt)H \xrightarrow{HMDS} (EtO)_2CHP(OSiMe_3)OEt$$

(1) (2)

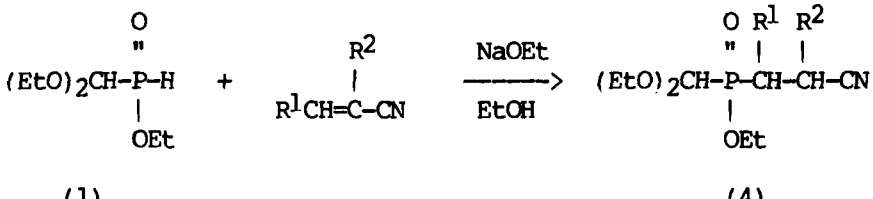
An alternative synthon employing similar protection of the P-H function has been prepared in quantitative yield from the reaction of methyl dichlorophosphine and triethylorthoformate.

$$CH_3PCl_2 + 2(EtO)_3CH \longrightarrow (EtO)_2CHP(O)(OEt)CH_3$$

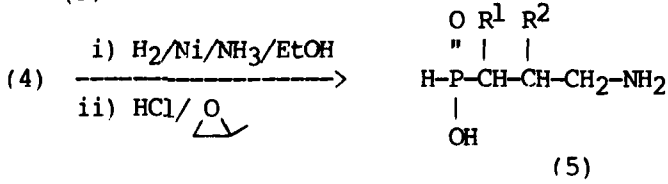
(3)

The methyl group in (3) can be selectively deprotonated and alkylated enabling a range of substituted phosphonous acids to be prepared.

These three reagents have been successfully used in the synthesis of substituted phosphonous analogues of GABA. Thus (1) adds to α,β-unsaturated nitriles to give the phosphinates (4). An appropriate choice of hydrogenation conditions allowed selective reduction of the nitrile, whilst preserving the protected phosphonous acid. Deprotection was achieved by refluxing in mineral acid.



(1) (4)

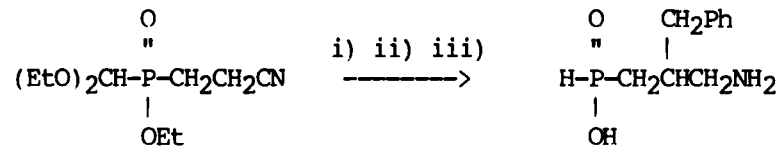


(5)

R^1 = H, CH_3, C_6H_5, 4-ClC_6H_4; R^2 = H, CH_3

Many α-substituted acrylonitriles are unstable and polymerise readily and this method is unattractive for the synthesis of 2-substituted analogues.

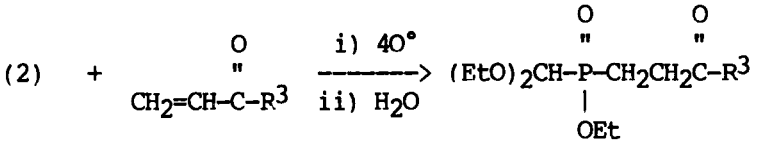
The protected phosphonous acid function in (4) where R^1 = R^2 = H facilitated the introduction of substituents into the 2-position. This was demonstrated with benzylbromide, by a regioselective deprotonation and alkylation.



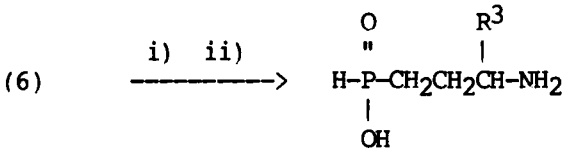
1) LDA/THF/-78°/$PhCH_2Br$, ii) $H_2/Ni/NH_3/EtOH$, iii) HCl

The introduction of aryl groups into this position is achieved by a different method discussed below.

The introduction of substituents into the 3-position has been achieved by initial reaction of the synthon (2) with α,β-unsaturated ketones. The keto phosphinates (6) are then reductively aminated and deprotected to give the products (7).



(6)

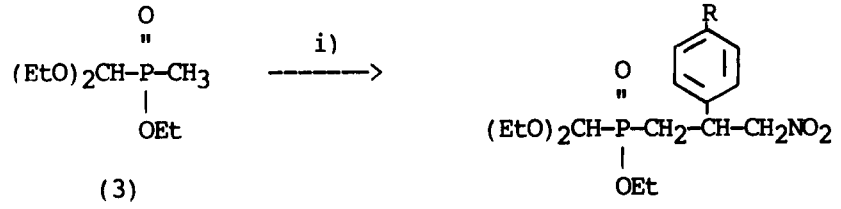


(7)

$R^3 = CH_3$, $4\text{-}ClC_6H_4$

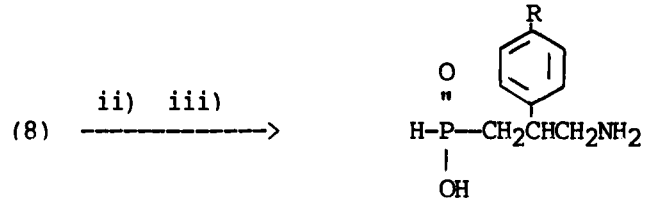
i) $NaBH_3CN/NH_4OAc$ ii) HCl

The preparation of 2-aryl substituted analogues was achieved using the protected methylphosphonous acid synthon (3). Generation of the anion and Michael addition to a range of β-nitrostyrenes gave the γ-nitrophosphinates (8). Subsequent reduction and acid hydrolysis gave the products (9).



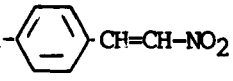
(3)

(8)



(9)

R = H, Cl, OCH_3

i) 1.2 eq. LDA/THF/-78°/1 hr. then 

ii) H_2/Ni/EtOH, iii) HCl 

Biological studies on these compounds within CIBA-GEIGY have confirmed that phosphonous acids are excellent mimics for carboxylic acids capable of more powerful binding to a receptor than the natural agonist. Thus, the phosphonous analogue of GABA has the highest selective binding to the GABA B receptor so far reported [IC_{50} = 1 x 10^{-9}M][6] and some 6000 times greater than the phosphonic analogue. In addition, compounds bearing aryl groups in the 2-position possess a similar biological profile to the CIBA-GEIGY product LIORESAL ®, and their analgesic, anti-convulsant and muscle-relaxant properties are currently under study.

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