Synthesis of Two New Azabicyclophosphinic Acids as Constrained Analogues of TPMPA

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Abstract: Utilization of the Polniaszek reagent $Cl_2PNi\text{-}Pr_2/AlCl_3$ was used on amino dienes to generate new azabicyclophosphinic acid as constrained analogues of TPMPA.

Key words: phosphorus, bicyclic compounds, cyclizations, medicinal chemistry, receptors

γ-Aminobutyric acid, GABA, is the major inhibitory neurotransmitter in the mammalian central nervous system. Currently, three classes of GABA receptors have been characterized: two ion channels ($GABA_A$ and $GABA_C$) and a GPCR ($GABA_B$). The $GABA_C$ receptors are composed of three subunits ρ1, ρ2 and ρ3 and the ρ1 $GABA_C$ subunit is essentially expressed in the eye. In addition, $GABA_C$ receptors appear to be involved in a number of inherited diseases of the eye. These aspects have focused interest on the $GABA_C$ receptor as a novel therapeutic target.[1]

A number of compounds have been synthesized in order to get inhibitory effects on ρ1 $GABA_C$ receptors. So far the best compound in the area seems to be TPMPA[2] with a K_i of 3.2 μM. Reported SAR on $GABA_C$ is limited. The trend is that $GABA_C$ binding affinity seems to require a basic and an acidic group ideally arranged in the median plane of the molecule separated by roughly three carbons.[3] TPBuPA[4] (where the methyl is replaced by a butyl chain) is reported to be 10 times less potent than TPMPA (Figure 1).

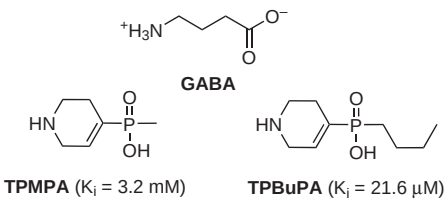
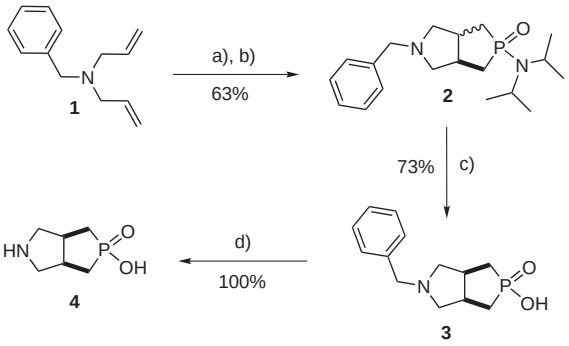


Figure 1 Structure of GABA, TPMPA and TPBuPA.

Increasing the size of the alkyl chain on the phosphorus moiety thus seems not favorable in terms of activity. Imbedding the phosphinic acid moiety into a bicyclic structure appears to fulfill the documented SAR requirements in terms of planarity of the molecule. Such compounds due to their high conformational constraints would also allow the refinement of topological features necessary for $GABA_C$ binding. A number of such structures can be envisaged based on 5,5- or 6,5-bicycles and differing in the position of the phosphorus atom. We wish to report in this letter our efforts towards the syntheses of such novel azabicyclophosphinic acids.

The general approach for the synthesis of the azabicyclophosphinic acids was based on a [4+1] cycloaddition between a diene containing the amino group and a phosphorus precursor. Such reactions are reported in the literature mainly using phosphorus tribromide.[5] This reaction is very slow, needing generally several days to several weeks. An alternative pathway was described by Polniaszek with the use of $(i\text{-Pr})_2NPCl_2$ in presence of $AlCl_3$ followed by oxidative work-up with saturated $NaHCO_3$ and a 0.2 M solution of EDTA to generate phosphinic amide.[6]

In order to access a 5,5-bicyclic system, we applied this cyclization type on the *N*-benzyl protected diallylamine. Cyclization was carried out at room temperature in CH_2Cl_2 for 16 hours. LC/MS analysis showed incomplete conversion. After refluxing one hour, complete conversion was observed. Oxidative work-up yielded to the bicycle **2** in a 63% isolated yield.[7] ^{31}P NMR showed a mixture of *cis* and *trans* isomers. The amide group was then hydrolyzed in 6 N HCl to afford the phosphinic acid **3** in a 73% yield as the *cis* isomer. Final hydrogenolysis was quantitative and gave free azabicyclophosphinic acid **4**[8] as a single isomer (Scheme 1).



Scheme 1 *Reagents and conditions*: a) i. $AlCl_3$, $Cl_2PNi\text{-}Pr_2$, CH_2Cl_2, –20 °C and then r.t. 1 h; ii. **2** at –20 °C, then r.t. 16 h and reflux for 1 h; b) 0.2 M EDTA–sat. $NaHCO_3$ (1:1), r.t., 5 h; c) HCl 6 N, reflux, 16 h; d) H_2, 20% Pd/C, EtOH.

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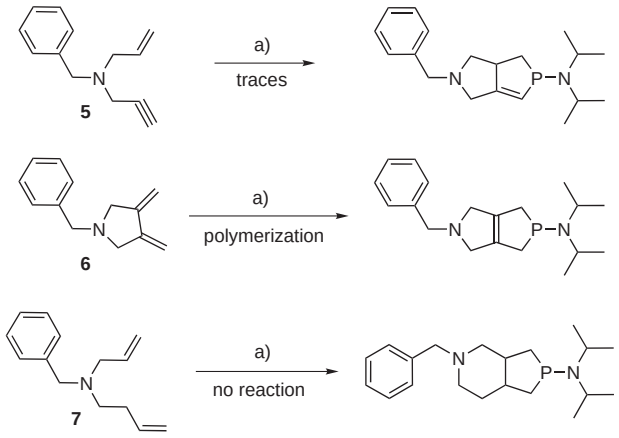
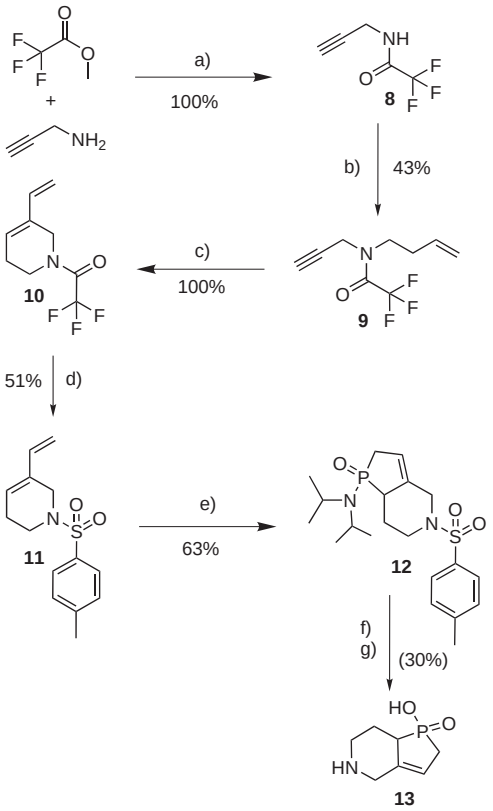
This cyclization was also applied to a more constrained starting material: *N*-benzyl-*N*-allyl-propargyl-amine **5**. Under cyclization conditions applied to **1**, only traces of the expected bicycle were observed by LC/MS even after refluxing several hours in CH_2Cl_2 or using a higher boiling solvent such as DCE. Protection of the acidic hydrogen of the acetylene by a trimethylsilyl group did not show any effect. Palladium chemistry on **5** led to the *N*-benzyl pyrrolidine **6** bearing two *exo*-methylenes.[9] Application of the cyclization conditions led to polymerization. A less constrained molecule *N*-benzyl-*N*-allyl butylamine **7** was then used in order to afford a 5,6-bicycle structurally closer to TPMPA. As previously described, no cyclization was observed in refluxing DCE (Scheme 2).



Scheme 2 *Reagents and conditions*: a) i. $AlCl_3$, $Cl_2PNi\text{-}Pr_2$, DCE, –20 °C and then r.t. 1 h; ii. **5** or **6** or **7** at –20 °C and then reflux for 16 h.

In order to access a 6,5-bicyclic system, butadiene derivative **11** was synthesized. Propargyl trifluoroacetamide **8** was obtained quantitatively from the condensation of propargyl amine and methyl trifluoroacetate. Then, under Mitsunobu conditions, *N*-propargyl-*N*-butene trifluoroacetamide **9** was obtained in a 43% yield. Ring-closure was then carried out with the Grubb's catalyst in order to access the corresponding butadiene in a quantitative yield. Due to its lability in subsequent steps, the trifluoroacetamide protecting group was exchanged for *p*-toluenesulfonyl amide by treatment of **10** with *p*-toluenesulfonyl chloride in presence of potassium carbonate in methanol–water. Applying cyclization conditions (no reflux was needed to ensure complete cyclization) led this time to the expected bicycle. After oxidative work-up, **12** was obtained in 63% isolated yield. Removal of the protecting group and hydrolysis of the phosphinic amide was achieved in one step by refluxing in 6 N HCl. Purification was realized by filtration of the crude mixture over DOWEX resin[10] to afford the free azabicyclophosphinic acid **13**[11] as a single compound. No rearrangement with migration of the double bond onto the bridge was observed under such harsh conditions (Scheme 3).



Scheme 3 *Reagents and conditions*: a) TEA, CH_2Cl_2, 0 °C, 1 h; b) PPh_3, DEAD, 3-buten-1-ol, THF, r.t., 12 h; c) Grubb's catalyst, CH_2Cl_2, r.t., 22 h; d) *p*-TsCl, K_2CO_3, MeOH–H_2O (7:3), r.t. for 3 h and then 50 °C for 1 h; e) i. $AlCl_3$, $Cl_2PNi\text{-}Pr_2$, CH_2Cl_2, –20 °C and then r.t. 1 h; ii. **11** at –20 °C and then r.t. 16 h; iii. 0.2 M EDTA–sat. $NaHCO_3$ (1:1), r.t., 5 h; f) HCl 6 N, reflux, 16 h; g) purification over DOWEX 50WX4 resin.

In conclusion, we have showed the synthesis of two new azabicyclophosphinic acids using $(i\text{-Pr})_2NPCl_2/AlCl_3$ as reagents for the formation of the phosphorus cycle as constrained analogues of TPMPA.

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(7) **Typical Procedure for Cyclization/Oxidation.** To a suspension of $AlCl_3$ (1.3 g, 10 mmol) in CH_2Cl_2 was added dropwise, at –20 °C and under N_2, $Cl_2PNi\text{-}Pr_2$ (2.0 g,10 mmol) in CH_2Cl_2. Then, the mixture was stirred at r.t. for 1 h. The mixture was cooled down to –20 °C and *N*-benzyl diallylamine (936 mg, 5 mmol) in CH_2Cl_2 was added dropwise. The mixture was allowed to warm up to r.t., stirred at r.t. for 16 h and refluxed for 1 h. The mixture was cooled down to 0 °C and 10 mL of a solution of 0.2 M EDTA–sat. $NaHCO_3$ (1:1) was added carefully. The mixture was then stirred at r.t. for 5 h. Then, 100 mL of H_2O were added and the aqueous phase was extracted several times with $CHCl_3$. The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuo to afford a crude yellow oil (2 g). Purification was achieved by flash chromatography over silica gel using EtOAc–MeOH (100:0 to 80:20) as eluent. After concentration of the fractions, a yellow paste (1.05 g, 63%) was obtained.

(8) ^{1}H NMR (400 MHz, D_2O): δ = 3.55 (m, 2 H), 3.03 (m, 2 H), 2.85 (m, 2 H), 1.82 (m, 2 H), 1.40 (m, 2 H).

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(10) Protocol for purification over DOWEX resin see: Dumond, Y. R.; Montchamp, J.-L. *J. Organomet. Chem.* **2002**, *653*, 252.

(11) ^{1}H NMR (400 MHz, D_2O): δ = 5.87 (d, *J* = 31.7 Hz, 1 H), 3.79 (d, *J* = 14.0 Hz, 1 H), 3.56 (d, *J* = 15.9 Hz, 1 H), 3.42 (dd, *J* = 12.8 Hz, *J* = 2.4 Hz, 1 H), 3.01 (m, 1 H), 2.30 (m, 1 H), 2.15 (m, 2 H), 2.00 (m, 1 H), 1.63 (m, 1 H).