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Synthesis of imidazole phosphinic acids as I4AA analogues

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Abstract—The $GABA_C$ receptor has been identified as a potentially attractive target involved in a number of eye diseases. TPMPA is the best antagonist reported so far. The synthesis of two new pharmacophores based on imidazole phosphinic acid core structure will be presented.

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 related ($GABA_B$). 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 an interest on the $GABA_C$ receptor as a novel therapeutic target.[1]

A number of compounds have been synthesized in order to get inhibitory effect on ρ1 $GABA_C$ receptors. So far, the best compound in the area seems to be TPMPA with a K_i of 3.2 μM. TPMPA[2] was designed by selecting the core structure of isoguvacine (a known $GABA_{A/C}$ ligand) in which the carboxylic acid was replaced by a phosphinic acid in order to increase activity and selectivity towards $GABA_C$. Following the same design, imidazole-4-acetic acid (I4AA), which is already known as a ρ1 $GABA_C$ antagonist/partial agonist[3] was selected as a template. Little is known about the $GABA_C$ receptor ligands' binding site but 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 and separated by roughly three carbons.[4] We wish to report herein the synthesis of two new classes of imidazole phosphinic acids **1** and **2**, as I4AA analogues, by replacing the carboxylic acid by a phosphinic acid and modulating the linker chain between the imidazole and the phosphinic acid (Fig. 1).

For the synthesis of the 4-imidazole phosphinic acid analogue **1**, commercial 4-carboxyimidazole was used as the starting point. Imidazole was protected with a trityl group in a 65% yield. Introduction of the phosphorus in a pseudo benzylic position was not possible by direct nucleophilic substitution of a phosphinate on activated imidazoles (–CH_2Br, –CH_2Cl or –CH_2OMs) most probably due to the high instability of these compounds. Therefore the phosphinic ester was introduced through a Pudovik condensation between aldehyde **4** and butyl

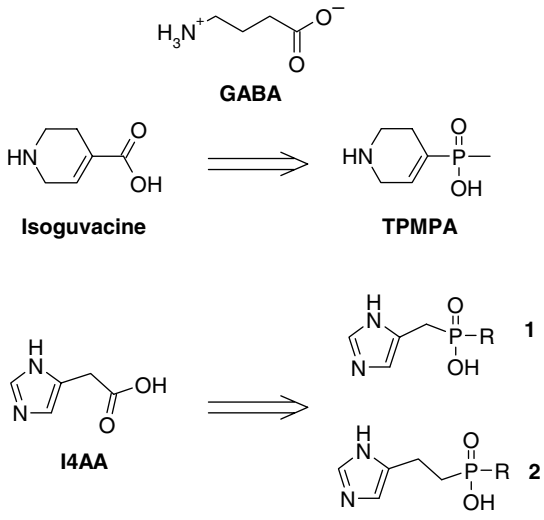

Figure 1. Structure of GABA, isoguvacine, TPMPA, I4AA and imidazole phosphinic acids **1** and **2**.

Keywords: Phosphinic acid; Imidazole; GABA; TPMPA.
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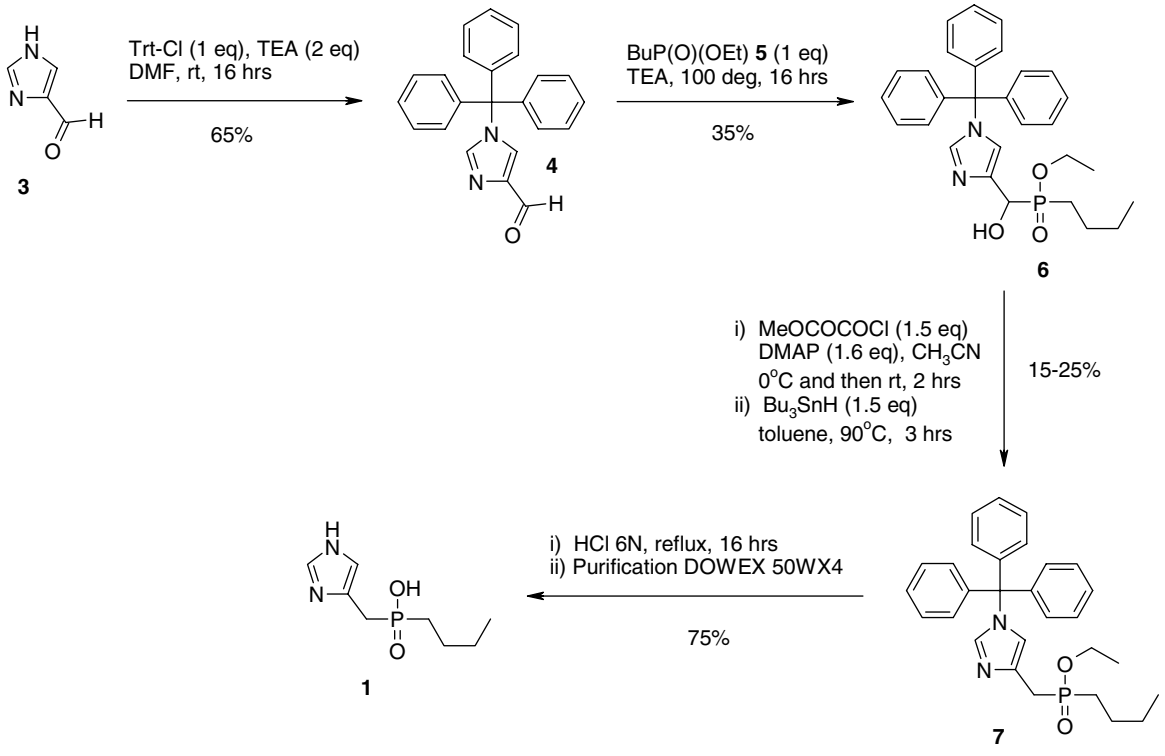
ethylphosphinate **5**[5] in neat triethylamine.[6] The corresponding imidazole phosphinic ester **6** was obtained in a moderate yield of 35%. Addition of a co-solvent such as toluene or changing the base did not improve the yield. Deoxygenation was realized by a modified Barton-type reaction as described by Kehler.[4] The deoxy derivative **7** was obtained in an isolated yield ranging from 15% to 25% together with 4-hydroxymethyl tritylimidazole, which was detected by LC/MS analysis. Utilization of diphenylchlorosilane in the presence of catalytic amounts of indium chloride as an alternative pathway for this deoxygenation, gave no reaction.[7] Finally, removal of the acid labile groups was carried out in refluxing HCl 6 N. Purification was achieved by filtration over DOWEX resin[8] to afford 4-imidazolmethyl-*n*-butylphosphinic acid **1**[9] in a 75% yield (Scheme 1).

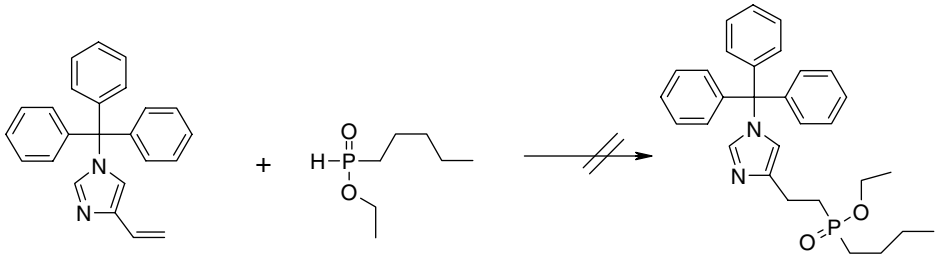
For the introduction of an ethylene spacer between the imidazole and the phosphinic acid, the first approach was based on the addition of a phosphinate onto a double bond as previously reported.[10] This reaction however did not proceed between vinyl tritylimidazole[11] and **5** under several conditions (Scheme 2).

As an alternative pathway, nucleophilic substitution of a phosphinate on an alkyl bromide was chosen. *N*-Benzyl imidazole carboxylic acid **8** was used as the starting point. After esterification under acidic catalysis, ester **9** was reduced with LAH to the corresponding alcohol. Bromination of the alcohol was achieved with triphenyl phosphine and bromine in low yield. This was probably due to the relative instability of **11**, which had to be used quickly for the next step. Four equivalents of phosphinate **5** were used for the nucleophilic substitution affording compound **12** in a 65% yield. Removal of the benzyl group by hydrogenation over Pd/C was quantitative. Finally, imidazole phosphinic acid **2**[12] was obtained in a 61% isolated yield after refluxing in HCl 6 N and purification over DOWEX resin (Scheme 3).

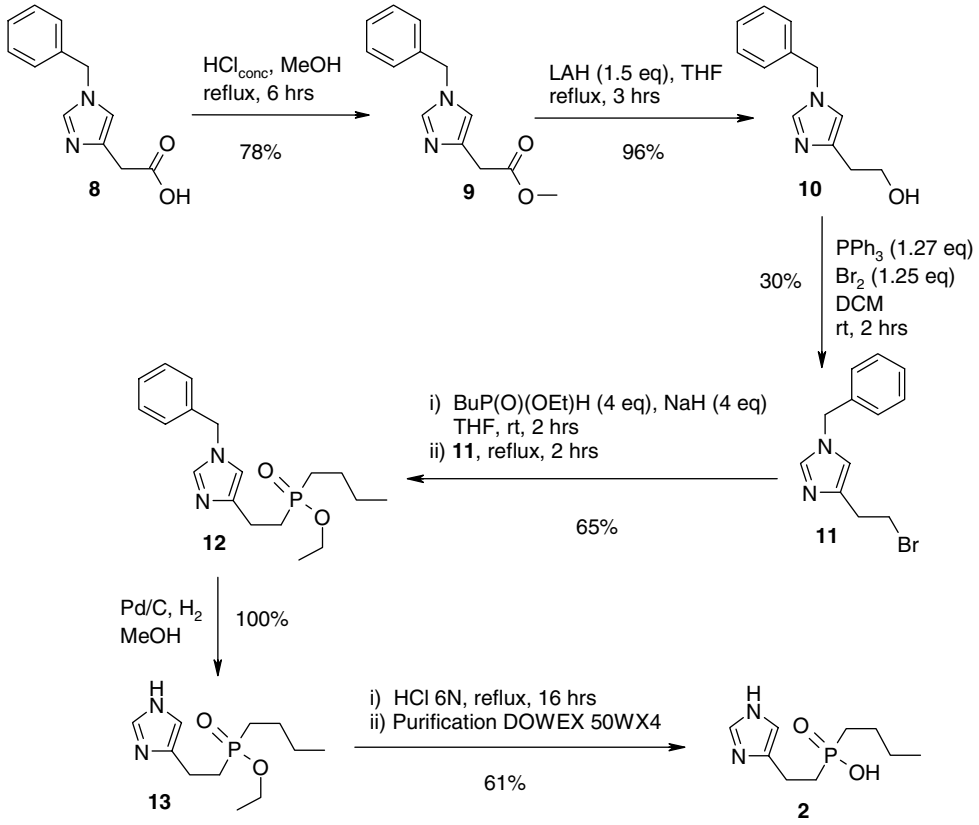
In conclusion, using I4AA as template, the carboxylic group has been replaced by a phosphinic group leading



Scheme 1. Synthesis of imidazole phosphinic acid **1**.



Scheme 2. Addition of phosphinate onto double bond.



Scheme 3. Synthesis of imidazole phosphinic acid **2**.

to the synthesis of two new imidazole phosphinic acids. Biological results will be reported in due course.

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References and notes

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12. ^{1}H NMR (400 MHz, D_2O): δ 7.50 (s, 1H), 6.82 (br s, 1H), 3.92 (m, 2H), 2.66 (m, 2H), 1.97 (m, 2H), 1.62 (m, 2H), 1.36 (m, 4H), 1.21 (t, $J = 7.1$ Hz, 3H), 0.86 (t, $J = 7.0$ Hz, 3H).