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Phosphinyl analogues of hydroxybupropion: (±)-2-aryl-3,3,5,5-tetramethyl-[1,4,2]-oxazaphosphinanes

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Abstract—Analogous structures in phosphinate series of hydroxybupropion **2**, that is, (±)-2-aryl-3,3,5,5-tetramethyl-[1,4,2]-oxazaphosphinanes **8**, are prepared according to a two step sequence: addition–cyclization reaction from methyl hypophosphite and oxazolidine **6**, followed by a pallado-catalyzed arylation of P–H bond from oxazaphosphinane **7**.

Wellbutrin® and Zyban® are trademarks of drugs used, respectively, for the treatment of depression and tabagism, with an active and identical ingredient, the acyclic compound named Bupropion **1**. The latter is metabolized by humans into an active and major arylmorpholinol compound named hydroxybupropion **2** (Fig. 1),[1] whose (2*S*,3*S*)-hydroxy-isomer **2** revealed to be, in vitro, about three and half-fold more potent as commercial Bupropion towards the enzyme responsible for the capture of noradrenaline.[2]

From a structural analogy, phosphinate analogues of 2-arylmorpholinols[3] could be also efficient candidates to inhibit noradrenaline uptake,[4] and thus, be subjected to evaluation for a treatment of depression and attention deficit hyperactivity disorder (ADHD).

Recently, we reported a stereoselective access to original [1,4,2]-oxazaphosphinanes **3**–**5** having at least three well-defined stereogenic centres, and structurally close to hydroxybupropion **2**.[5a,b,e–g] Here, we wish to describe the first synthesis of methyl analogues, that is, tetramethyl derivatives **8**. The preparation of these compounds was envisioned according to a similar pathway previously depicted for **3**–**5**.[5g] The synthetic concept was based on two steps, firstly, a nucleophilic attack

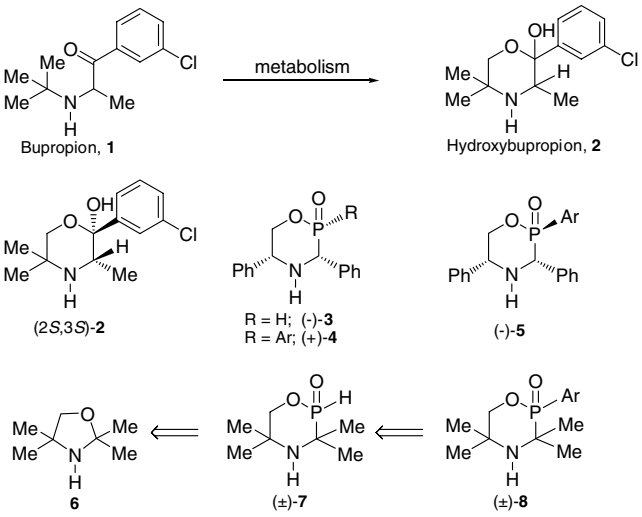

Figure 1. Antidepressants drugs: Bupropion **1** and arylmorpholinol **2**, phosphinyl analogues (diphenyl and tetramethyl series).

of methyl hypophosphite on oxazolidine **6**, followed by an intramolecular cyclization to **7** having a reactive P–H bond. The electrophilic character of **6** was previously described by Levin et al. in the case of its reaction with dimethyl phosphonate, but it was never applied to phosphinic precursors.[6] Finally, a pallado-catalyzed arylation from the oxaphosphinane **7** allowed to form the expected product **8** (Fig. 1).

2,2,4,4-Tetramethyl-1,3-oxazolidine **6** is easily accessible from a procedure, described by Hintze and Hoppe,

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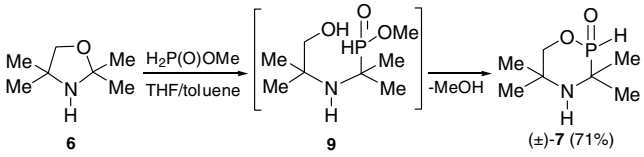
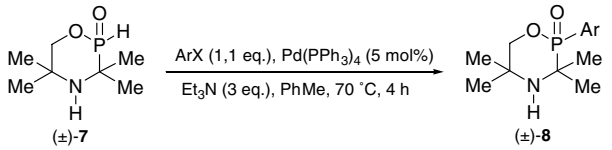
which consisted in the condensation of 2-methyl-2-aminopropanol and acetone in dichloromethane with the removal water using a Dean–Stark apparatus.[7] After addition of 1 equiv of oxazolidine **6** to methyl hypophosphite (prepared in situ from the corresponding acid with 4 equiv of trimethyl orthoformate in toluene/THF (2:1)[8]) for 18 h at room temperature, oxazaphosphinane **7** was generated with an approximate 80% yield, evaluated by ^{31}P NMR ($\delta = 41.3$ ppm). Contrary to the process previously described for oxazaphosphinane **3**, preparation of methyl analogue **7** did not require a catalysis by potassium *tert*-butoxide in order to achieve cyclization of phosphinate opened form **9**. In contrast to the diphenyl series, compound **9** could not be clearly identified in ^{31}P NMR. A possible explanation might be the well-known Thorpe–Ingold effect.[9] Indeed, the presence of four methyl groups on the open chain **9** should allow the hydroxyl function to be spatially closer to the reactive phosphinate than in the case of two phenyl groups. Thus, it should facilitate the intramolecular cyclization of **9**, which would prevent its visualization through ^{31}P NMR. After an aqueous work-up, followed by vacuum distillation, oxazaphosphinane **7** was isolated as a racemic mixture in 71% yield (Scheme 1). Unfortunately, all attempts to get monocrystals from the free amine or its ammonium salt failed, preventing us to assign its conformation by an X-ray experiment.



Scheme 1. 2-Hydrogeno-2-oxo-1,4,2-oxazaphosphinane **7**.

Subsequently, the P–H bond in **7** was arylated through a pallado-catalyzed reaction, using conditions depicted in Scheme 2.[5c–g] Various arylated compounds **8a**–**f** in tetramethyl series and analogues of hydroxybupopion **2** were thus obtained as mixtures of two enantiomers in yields ranging from 57% to 95% (Table 1).

Compound **8f** gave monocrystals in diethyl ether/hexanes (1:2); and the six-membered ring showed a preference for a chair conformation, having *meta*-chlorophenyl group in equatorial position and the phosphinyl bond in axial position (Fig. 2). Ammonium salt of (2*S*,3*S*)-arylmorpholinol **2** give similar result with aryl function in equatorial position and hydroxyl in axial position.[10]



Scheme 2. Arylation of 2-hydrogeno-2-oxo-[1,4,2]-oxazaphosphinane (±)-**7**.

Table 1. Arylation of 2-hydrogeno-2-oxo-[1,4,2]-oxazaphosphinane (±)-**7**

Final compound	Ar–X	Yield[a] (%)
(±)-**8a**	Ph–I	74
(±)-**8b**	*p*-MeO–C_6H_4–I	61
(±)-**8c**	*p*-Br–C_6H_4–I	57
(±)-**8d**	*p*-NO_2–C_6H_4–I	95
(±)-**8e**	3,5-F_2–C_6H_3–Br	84
(±)-**8f**	*m*-Cl–C_6H_4–Br	94

[a] Isolated yields after purification by column chromatography on silica gel.

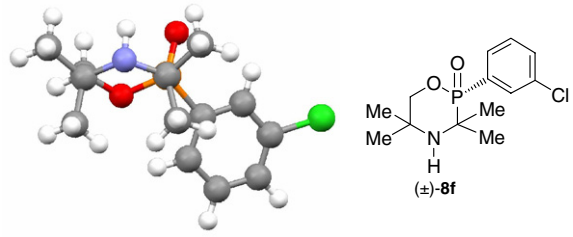


Figure 2. Chair conformation in the X-ray of (±)-**8f**.[11]

Several and novel 3,3,5,5-tetramethyl-[1,4,2]-oxazaphosphinanes have been thus obtained through a short sequence and from easily accessible starting materials, oxazolidine and methyl hypophosphite. We envisage to apply this strategy for the access to trimethylated derivatives, which are the exact analogues in phosphinate series of hydroxybupropion **2**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.014.

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