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Palladium-catalyzed cross-coupling reaction of anilinium hypophosphite with alkenyl bromides and triflates: application to the synthesis of GABA analogs

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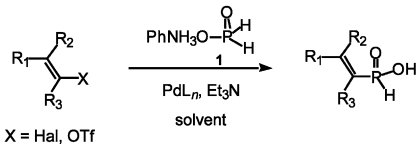
Abstract

Alkenyl bromides and triflates undergo palladium-catalyzed cross-coupling with anilinium hypophosphite to afford monosubstituted phosphinates (salts of alkenylphosphonous acids). The reaction is an extension of our previously reported methodology for the synthesis of aryl- and benzyl-phosphonous acids. Our preliminary results show that the best reaction conditions are observed with $Pd(OAc)_2$/dppp as a catalyst, in refluxing benzene or tetrahydrofuran. This novel P–C bond forming reaction is applied to the synthesis of (1,2,3,6-tetrahydropyridin-4-yl)-methylphosphinic acid (TPMPA), a selective competitive antagonist for $GABA_C$ receptors. The divergent synthesis proceeds through protected (1,2,3,6-tetrahydropyridin-4-yl)-phosphinic acid, a previously unknown isoguvacine-like GABA analog. This synthetic intermediate is also an ideal precursor to other biologically interesting GABA analogs. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Cross-coupling; Anilinium hypophosphite; Phosphinic acid; Palladium catalysis; GABA analogs

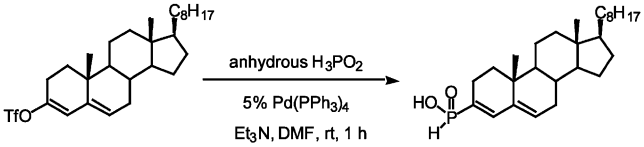
1. Introduction

As part of our ongoing efforts aiming at the preparation of biologically active phosphinic acids, we have undertaken the study of hypophosphites in organic synthesis [1]. Recently, we reported the Et_3B-initiated radical reaction of hypophosphite salts and esters at room temperature [1a,1b], and the palladium-catalyzed cross-coupling reactions of anilinium hypophosphite with aryl iodides, bromides, triflates, and benzylic chlorides [1c]. In order to further extend the range of accessible functionalized monosubstituted phosphinic acids (alkylphosphonous acids) derivatives, and the scope of our previously reported methodologies for P–C bond formation, we studied the Pd-catalyzed reaction of alkenyl halides with anilinium hypophosphite (Eq. (1)).



(1)

Although palladium-catalyzed cross-coupling reactions have become exceedingly important in the preparation of carbon–carbon, and carbon–heteroatom bonds, phosphorus–carbon bond formation has been mostly limited to the synthesis of phosphine and phosphonate derivatives [2]. In an effort to extend Pd-catalysis to produce monosubstituted phosphinic acids (phosphonous acids), the reaction between anilinium hypophosphite and alkenyl electrophiles was investigated. Herein, we report the successful preparation of alkenyl phosphinic acids via cross-coupling, and its application to the synthesis of GABA analogs.



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A literature survey revealed a single example of cross-coupling between anhydrous hypophosphorous acid and a steroidal dienyl triflate (Eq. (2)) [3]. Other methods to access alkenyl phosphinic acids rely on the reaction of organometallic nucleophiles (RZnX, RMgX, RLi) with chlorophosphines (PCl_3, $(EtO)_2PCl$) followed by hydrolysis [4], or Nifant'ev's peroxide-initiated radical reaction of hypophosphorous acid with alkynes [5]. These methods are generally not functional group tolerant as they proceed under strongly basic or strongly acidic conditions, respectively. Furthermore, Nifant'ev's protocol leads to an ca. 1:2 ratio of *cis*–*trans* isomers (22–69% combined yield, determined by ^{31}P-NMR). Multi-step reaction sequences have been employed in some cases [6]. A mild, one-step access to monosubstituted alkenyl phosphinic acid derivatives would be valuable since it avoids protection–deprotection schemes. We now report the successful cross-coupling of alkenyl halides with anilinium hypophosphite [7], and we demonstrate the usefulness of this reaction for the preparation of biologically active compounds.

2. Results and discussion

2.1. Reaction of anilinium hypophosphite with alkenyl halides

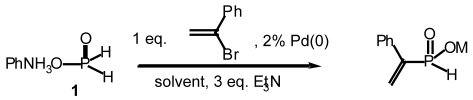
Based on our experience with aryl halides and related compounds [1c], we first investigated the reaction of alkenyl halides with anilinium hypophosphite. To our knowledge, alkenyl halides have never been employed in this type of reaction. Hypophosphorous derivatives are powerful reducing agents, particularly in the presence of transition-metal catalysts such as palladium (transfer hydrogenation) [8]. Suppression of the reductive pathway is an obvious difficulty which must be overcome to achieve good cross-coupling yields [1c]. While recognizing that a detailed understanding of the reaction mechanistic pathways would require further investigations, our previous observations of the influence of various reaction parameters in favoring cross-coupling versus reduction[1c] left us confident that this reaction could be developed.

Initial experiments using commercially available α-bromostyrene revealed a number of key variables for successful cross-coupling reaction. The choice of solvent affects the cross-coupling efficiency, highest yields being achieved in refluxing benzene or tetrahydrofuran (THF) (entries 12–17). Interestingly, this parameter differs in the case of aryl halides, where acetonitrile and DMF worked best [1c]. With the exception of THF (entry 12), reagent grade solvents were employed since anhydrous solvents did not afford significantly improved yields.

The choice of phosphine ligand was also important, and dppp (1,3-bis(diphenylphosphino)propane) was consistently superior to PPh_3 (entries 1 vs. 4, and 6 vs. 7 and 13 vs. 14) in suppressing the reductive pathways responsible for low cross-coupling yields. Significantly higher amounts of styrene were observed by capillary GC in runs using triphenylphosphine (for example, compare entry 1 vs. 3). The source of palladium had little effect, as $Pd(OAc)_2$ and $Pd_2(dba)_3$ were equally effective catalyst precursors (entries 16 vs. 17). Increasing the catalyst loading had also no significant effect (entry 4 vs. 3).

A potential side-reaction is the Michael-like addition of another molecule of hypophosphite to the initially formed alkenylphosphinic acid. Although a catalyzed process cannot be ruled out, this side reaction was suppressed by either using a slight excess of hypophosphite, or alternatively, keeping the reaction time short

Table 1
Influence of conditions on the palladium-catalyzed cross-coupling of anilinium hypophosphite with α-bromostyrene



Entry	Equivalent of **1**	Solvent [a]	Catalyst [b]	Yield [c]
1	2.2	CH_3CN	$Pd(PPh_3)_4$	37 [i]
2	1.2	CH_3CN	$Pd(PPh_3)_4$	19
3	2.2	CH_3CN	$Pd(OAc)_2$+dppp	61 [i]
4	2.2	CH_3CN [d]	$Pd(OAc)_2$+dppp	60
5	1.2	CH_3CN	$Pd(OAc)_2$+dppp	24
6	1.2	DMF [e]	$Pd(PPh_3)_4$	29
7	1.2	DMF [e]	$Pd(OAc)_2$+dppp	37
8	2.2	$ClCH_2CH_2Cl$	$Pd(OAc)_2$+dppp	24 [j]
9	2.2	$PhCH_3$	$Pd(OAc)_2$+dppp	46
10	1.2	$PhCH_3$ [e]	$Pd(OAc)_2$+dppp	47
11	1.2	dioxane [e]	$Pd(OAc)_2$+dppp	54
12	1.2	THF [f]	$Pd(OAc)_2$+dppp	90 [f]
13	1.2	C_6H_6	$Pd(PPh_3)_4$	59 [j]
14	2.2	C_6H_6	$Pd(OAc)_2$+dppp	88 [j]
15	1.2	C_6H_6	$Pd(OAc)_2$+dppp [g]	92 [j]
16	1.2	C_6H_6	$Pd(OAc)_2$+dppp	98 [j]
17	1.2	C_6H_6	$Pd_2(dba)_3$+dppp [h]	92 [j]

[a] Unless otherwise noted, all reactions were conducted at the reflux temperature, and in reagent grade solvent. Reaction times were 18–24 h in all cases. Concentration of α-bromostyrene was 0.2 M.

[b] 2 mol% $Pd(PPh_3)_4$ or 2 mol% $Pd(OAc)_2$+2.4 mol% $Ph_2P(CH_2)_3PPh_2$ (dppp) was used as catalyst.

[c] Yields were determined by ^{31}P-NMR analysis of the crude reaction mixtures.

[d] 5 mol % $Pd(OAc)_2$+10 mol% $Ph_2P(CH_2)_3PPh_2$ (dppp).

[e] Conducted at 85 °C.

[f] Anhydrous THF was employed. (If reagent grade THF is used, the yield decreases to 75%.)

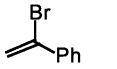
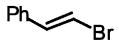
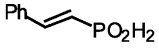
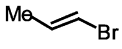
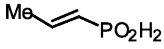
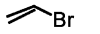
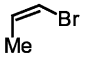
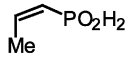
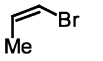
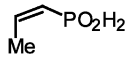
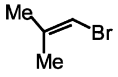
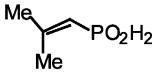
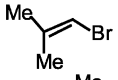
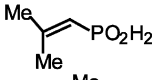
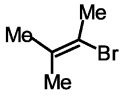
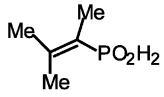
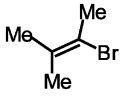
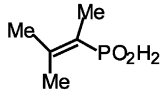
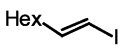
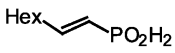
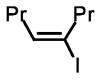
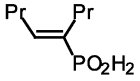
[g] 4 mol% dppp was used.

[h] 1 mol% $Pd_2(dba)_3$+2.4 mol% dppp.

[i] Styrene was detected by capillary GC chromatography. Yields were determined using an internal standard: entry 1, 30%; entry 3, 14%.

[j] Bis-addition product (Michael-like) formation: entry 8, 30%; entry 9, 36%; entry 14, 7%; entries 13 and 15–17, $<2\%$ (NMR).

Table 2
Palladium-catalyzed cross-coupling of anilinium hypophosphite with alkenyl halides

Entry	Alkenyl Halide	Product	^{31}P NMR yield[b] %	Isolated yield[c] %
1			98	67
2			85	75
3			94	60
4			85[d]	-
5			64[d]	-
6			21[d]	-
7			46[d,e]	-
8			27	-
9			78[e]	25
10			< 2	-
11			45[e]	23
12			59	17
13			17	-

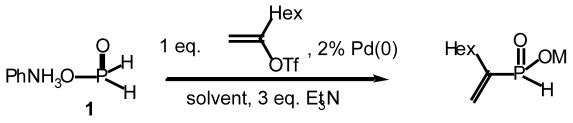
[a] All reactions were conducted in refluxing reagent grade benzene, except for entry 5 which was conducted in an Ace pressure tube at 85 °C. Reaction times were 16–24 h in all cases. Concentration of alkenyl halide was 0.2 M. Unless otherwise noted, 2 mol% $Pd(OAc)_2$+2.4 mol% $Ph_2P(CH_2)_3PPh_2$ (dppp) was used as catalyst. [b] Yields were determined by ^{31}P-NMR analysis of the crude reaction mixtures. [c] Isolated in ca. 90% purity after extraction (see Section 4). [d] Identified and characterized as the crude salt due to high solubility in water. [e] dppf was used instead of dppp.

when employing an excess of hypophosphite [9] (Table 1).

In agreement with our earlier work with aryl electrophiles, symmetrical phosphinic acids ($R_2P(O)OH$) did not form, indicating the much higher reactivity of hypophosphite salts ($MOP(O)H_2$) over the alkylphosphinate products (RP(O)(OM)H) in the cross-coupling reaction. Such selectivity is all the more important since symmetrically disubstituted phosphinic acids are often undesired side-products in the synthesis of monosubstituted phosphinic acids.

Once the reaction parameters delineated, other alkenyl halides were subjected to the optimized reaction conditions. The results are shown in Table 2. Isolated yields were not optimized: after a simple extractive work-up the corresponding monosubstituted alkenylphosphinic acids were obtained (usually around 90% purity). Low isolated yields reflect the very high water solubility of the products. In such cases (Table 2, entries 4–7), the products were only characterized as the crude salt by concentrating the reaction mixture. Variously substituted alkenyl bromides could be accommodated (Table 2, entries 1–5). However, steric hindrance due to *Z*-substitution required a ligand switch from dppp to 1,1′-bis(diphenylphosphino)ferrocene (dppf) (entries 6 vs. 7, 8 vs. 9, and 10 vs. 11). The stereochemical integrity of the alkene in the product was established by ^{1}H-NMR and, when possible, by comparison with known samples [5].

Table 3
Influence of conditions on the palladium-catalyzed cross-coupling of anilinium hypophosphite with 2-trifluoromethanesulfonyloxy-1-octene [a]



Entry	Time	Equivalent of **1**	Solvent	Catalyst [b]	Yield [c]
1	24	1.2	CH_3CN	$Pd(OAc)_2$+dppp	<2
2	7	1.2	DMF	$Pd(OAc)_2$+dppp	5–10
3	7	1.2	THF	$Pd(OAc)_2$+dppp	67
4	2	1.2	C_6H_6	$Pd(OAc)_2$+dppp	69
5	24	2.0	C_6H_6	$Pd(OAc)_2$+dppp	44 [d]
6	6	1.2	C_6H_6	$Pd(OAc)_2$+dppf	56
7	7	1.2	C_6H_6	$Pd(OAc)_2$+BINAP	42
8	24	1.2	C_6H_6	$Pd(PPh_3)_4$	58

[a] All reactions were conducted at the reflux temperature, and in reagent grade solvent. Triflate concentration was 0.2 M.
[b] Catalyst: 2 mol% $Pd(OAc)_2$+2.4 mol% diphosphine ligand, or 2 mol% $Pd(PPh_3)_4$.
[c] Yields were determined by ^{31}P-NMR analysis of the crude reaction mixtures.
[d] The bis-addition product (Michael-like) was also present in 22% yield (NMR).

While we have not extensively studied the reaction of alkenyl iodides and chlorides, some preliminary results were obtained. In general, iodides reacted sluggishly and erratically (entries 12 and 13, Table 2), while chlorides remained unreactive (results not shown). In the case of entry 13 we established by capillary GC that most of the mass balance was unreacted vinyl iodide, and not a reduction product. Limited attempts at using silver additives were unsuccessful.

2.2. Reaction of anilinium hypophosphite with alkenyl triflates

Next we investigated alkenyl triflates as electrophilic partners under the conditions we developed for alkenyl bromides. Although not providing much detail, Holt's single literature precedent [3] (Eq. (2)) suggested that such a reaction might be successful. Some data are shown in Table 3 for 2-trifluoromethanesulfonyloxy-1-octene. The reaction does proceed in reasonable yield, but appears even more sensitive than with alkenyl bromides (for example, compare entry 2, Table 2 with entry 4, Table 3). The choice of solvent is especially important, as acetonitrile was completely unsatisfactory (entry 1, Table 3), and DMF marginal (entry 2, Table 3) in contrast with Holt's report [3]. As in the case of alkenyl bromides, THF and benzene were once again optimum.

Bis-addition, through cross-coupling and subsequent Michael addition, was observed more extensively than in the case of bromides (entry 5, Table 3). The reaction did proceed slowly at room temperature to deliver 40% yield in 24 h, but this did not evolve further beyond 1 day. Again, dppp appears to be the best ligand, even if other ligands can be employed.

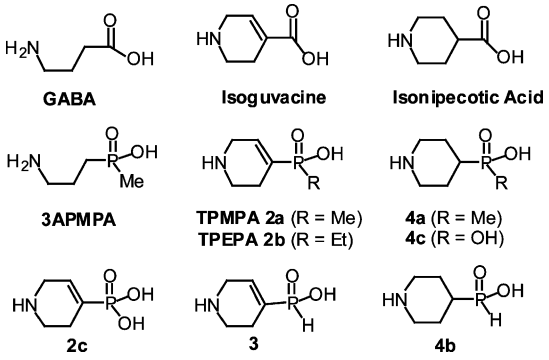
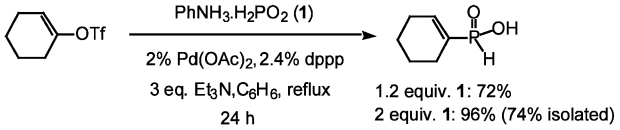


Fig. 1. Structures of GABA and some of its analogs.

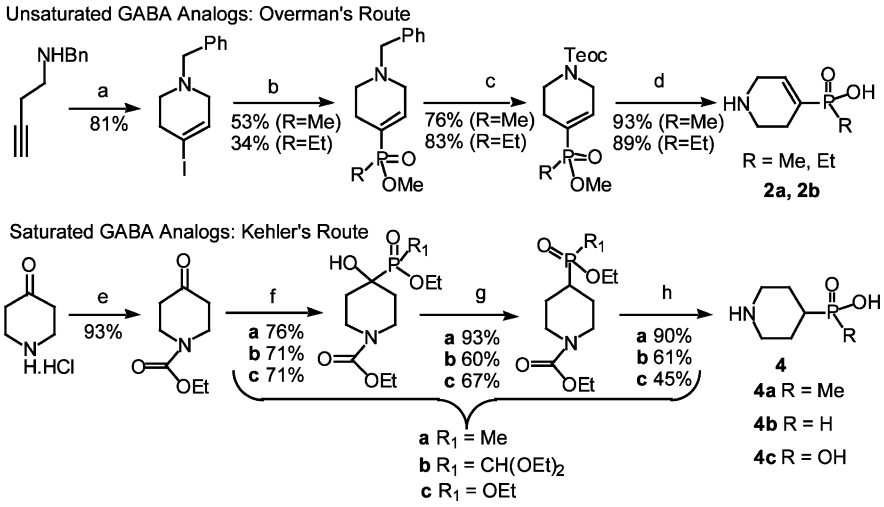
When cyclohexenyl triflate was reacted under our standard conditions (Eq. (3)), we were rewarded with an excellent yield of cross-coupling, suggesting that this, and Holt's steroidal triflate [3] are much better substrates than 2-trifluoromethanesulfonyloxy-1-octene. It also provided an encouraging precedent for the anticipated application of our methodology to the synthesis of GABA analogs.



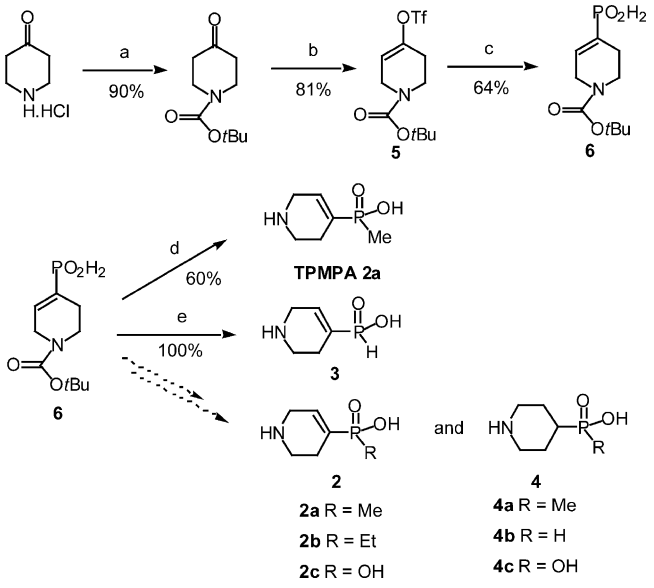
(3)

2.3. Application to the synthesis of GABA analogs

Since we are involved in the development of new methodology for the synthesis of organophosphorus compounds [1], and particularly biologically active ones,



Scheme 1. Literature syntheses of tetrahydropyridine-4-ylphosphinic acids (**2a**,**b**), and piperidine-4-ylphosphinic acids (**4a**-**c**)[a]. [a]See [11,12]. (a) CH_2O, NaI, RSO_3H, H_2O. (b) $RP(O)(OMe)H$, $Pd(PPh_3)_4$, DABCO, toluene, 85 °C. (c) $TMSCH_2CH_2OC(O)Cl$, toluene, r.t. (d) (i) 48% HBr, AcOH, 95 °C, (ii) Dowex 50 H^+. (e) EtOC(O)Cl, NaOH, Et_2O, H_2O. (f) $R_1P(O)(OEt)H$, Et_3N, 100 °C. (g) (i) MeOC(O)C(O)Cl, DMAP, CH_3CN, r.t.; (ii) Bu_3SnH, AIBN, toluene, 90 °C. (h) Concd. HCl, reflux.



Scheme 2. Synthetic approach to phosphinyl GABA analogs. (a) BOC_2O, Et_3N, DMF, r.t. (Ref. [16]). (b) (i) LDA, THF, −78 °C (ii) $PhNTf_2$, −78–0 °C (Ref. [14]). (c) $PhNH_3 \cdot H_2PO_2$ (**1**), $Pd(OAc)_2$, dppp, Et_3N, C_6H_6, reflux. (d) (i) DBU, MeI, TMSCl, −78 °C to r.t.; (ii) Dowex 50 H^+. (e) Concd. HCl, reflux.

we then turned our attention to the synthetic application of our reaction. Our cross-coupling provides an expeditious entry into the synthesis of GABA (4-aminobutyric acid) analogs.

GABA, a naturally-occurring inhibitory neurotransmitter, plays a key role in neuronal chemistry, and several types of GABA receptors have been identified [10]. Many GABA analogs have been studied and some have been designed for the treatment of disorders related to the central nervous system (CNS). A few representative GABA analogs are shown in Fig. 1. A few years ago, (1,2,3,6-tetrahydropyridin-4-yl)-methylphosphinic acid (TPMPA, **2a**) was reported as the first selective antagonist for $GABA_C$ receptors [11]. In 1998, saturated phosphinate-based GABA analogs **4** related to isonipecotic acid (Fig. 1) were also synthesized [12a], and their biological activities have been disclosed recently [12b,12c].

The literature syntheses of TPMPA (**2a**), the homologous TPEPA (**2b**), and the saturated phosphinates **4** are presented in Scheme 1 [11a,12]. Overman prepared the unsaturated analogs **2** via a key palladium-catalyzed cross-coupling reaction between an iodoalkene and alkylphosphinate esters [11a]. A slight improvement in the key step has since been reported [13]. Kehler prepared the piperidin-4-ylphosphinates (**4**) through a carbonyl addition of alkylphosphinate esters followed by radical deoxygenation [12].

Our approach (Scheme 2) relies on a much more divergent synthesis which can lead to structurally diverse GABA analogs. Following our conditions, the palladium-catalyzed cross-coupling of anilinium hypophosphite (**1**) with the known triflate **5** [14] affords intermediate **6** in 64% yield (Scheme 2). To our knowledge, the cross-coupling reaction of alkylphosphinate esters ($RP(O)(OR')H$) with alkenyl (and aryl) triflates is unknown [2] so that an Overman-like strategy could not be used with triflate **5**. In addition, compound **6** is ideally suited for further elaboration through a variety of methods, since the phosphinylidene group (P(O)H) can undergo numerous functional group transformations [15]. Indeed, monosubstituted phosphinic acids (phosphonous acids) are flexible precursors to access other organophosphorus compounds of synthetic or biological interest (disubstituted phosphinates, phosphonates, and phosphines). For instance, Arbuzov-like

reaction of **6** with methyl iodide and subsequent cleavage of the BOC protecting group afforded TPMPA **2a** in good overall yield. Cleavage of intermediate **6** directly afforded compound **3**, a novel GABA analog related to isoguvacine (Fig. 1). Other simple transformations of **6** could lead to a family of analogs, for example through hydrogenation or oxidation, en route to compounds **4** and **2c**, respectively [15]. The biological activity of **3**, and the design and synthesis of other GABA analogs will be reported in due course.

3. Conclusion

A novel palladium-catalyzed P–C bond forming reaction is described and applied to the preparation of GABA analogs. Alkenyl bromides and triflates react stereospecifically with anilinium hypophosphite in the presence of a catalytic amount of $Pd(OAc)_2$/dppp, whereas alkenyl iodides and chlorides do not react satisfactorily under comparable conditions. The reaction is also sensitive to the structure of the electrophiles (steric hindrance due to *Z*-substitutents), and the nature of the catalyst (ligand). Palladium tetrakis(triphenylphosphine) was generally a poor catalyst as competing reductive pathways which lead to a decrease in cross-coupling yield were usually observed. Whereas various solvents can be employed, THF and benzene appeared most satisfactory.

A divergent route to phosphorus-containing GABA analogs was also developed. The known $GABA_C$ antagonist **2a** was prepared expeditiously, and under mild conditions. The synthesis proceeds through the readily functionalized intermediate **6**, which is an ideal precursor to a family of GABA analogs, and particularly the novel phosphonous acid (**3**).

Further investigations will focus on increasing the scope of this cross-coupling reaction and its application to the synthesis of phosphinic acids of medicinal interest. The development of the palladium-catalyzed cross-coupling reactions of anilinium hypophosphite, along with our recently disclosed room temperature radical reaction of hypophosphorous derivatives, provide new methodology for the synthesis of structurally varied and functionalized phosphinic acids, under mild conditions.

4. Experimental

4.1. General chemistry

^{1}H-NMR spectra were recorded on a Varian XL-300 spectrometer. Organic solutions of products were dried over $MgSO_4$, and filtered. Other details have been provided elsewhere [1].

4.2. Reagents and solvents

Unless otherwise noted, HPLC grade or reagent grade C_6H_6, $C_6H_5CH_3$, dioxane, DMF, and 1,2-dichloroethane were used throughout. When anhydrous solvents or reagents were used, they were prepared as follows: Et_3N was distilled from CaH_2 and stored under N_2 over activated 4A molecular sieves; THF was distilled under N_2 from sodium benzophenone ketyl, and used immediately; C_6H_6 and CH_2Cl_2 were distilled immediately before use, from CaH_2 under N_2. Anhydrous MeCN and DMF were obtained after drying over activated 3A molecular sieves, and were stored under N_2. Catalysts and ligands were purchased from Aldrich or Strem and used as received. *N*-(*tert*-Butoxycarbonyl)-4-piperidone [16], *tert*-butyl-1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate [14], 1-cyclohexen-1-yl-triflate [17], 2-trifluoromethanesulfonyloxy-1-octene [18], *trans*-1-iodo-1-octene [19], *trans*-1-bromo-1-octene [20], and *E*-4-iodo-4-octene [21] were prepared as described in the literature. Anilinium hypophosphite (**1**) was prepared as previously described by us [1].

4.3. ^{31}P-NMR yield measurements

NMR yields were determined by integration of all the ^{31}P signals in the crude reaction spectrum, as described previously [1]. The extent of reduction was determined by integration of hypophosphite oxidation products (MH_2PO_3, and $M_2H_2P_2O_5$), and in selected cases, the identity of the organic reduction products was checked by ^{1}H-NMR and/or capillary GC. Bis-addition products (Michael-like) were identified by their characteristic J_{PCCP} couplings.

4.4. Preparation of (1-phenyl-vinyl)-phosphinic acid. Representative procedure

A solution of α-bromostyrene (0.366 g, 2 mmol), anilinium hypophosphite (**1**) (0.382 g, 2.4 mmol), anhydrous Et_3N (0.84 ml, 6 mmol), palladium acetate (9.0 mg, 0.04 mmol), and dppp (19.8 mg, 0.048 mmol) in reagent grade C_6H_6 (10 ml) was heated at reflux for 19 h. The reaction mixture was concentrated under vacuum, diluted in water, washed with Et_2O, and acidified with 1 M aq. $KHSO_4$ saturated with NaCl. The resulting aq. phase was extracted with EtOAC (3 ×). The combined organic fractions were dried, filtered, and concentrated under vacuum to afford the title compound in 67% isolated yield: ^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 12.37 (br, 1 H), 7.4–7.5 (m, 2 H), 7.2–7.4 (m, 3 H), 7.30 (d, $J = 571$ Hz, 1 H), 6.16 (d, $J = 46$ Hz, 1 H), 6.14 (d, $J = 25$ Hz, 1 H); ^{13}C-NMR ($CDCl_3$): δ 142.3 (d, $J_{PC} = 124$ Hz), 135.1 (d, $J_{PCC} = 13$ Hz), 129.3 (d, $J_{PCC} = 13$ Hz), 128.7 (2 C), 128.6, 127.3 (d, $J_{PCCC} = 6$

Hz, 2 C); ^{31}P-NMR ($CDCl_3$): δ 25.7 (ddd, $J = 571$ Hz, $J = 46$ Hz, $J = 24$ Hz).

4.5. Characterization of the water soluble products as the salt: preparation of triethylammonium vinyl-phosphinate [5b]

A solution of vinyl bromide (1 M in THF, 2 ml, 2 mmol), anilinium hypophosphite (0.382 g, 2.4 mmol), anhydrous Et_3N (0.84 ml, 6 mmol), palladium acetate (9.0 mg, 0.04 mmol), and dppp (19.8 mg, 0.048 mmol) in reagent grade C_6H_6 (8 ml) was heated in a sealed tube, at 85 °C for 19 h. The reaction mixture was concentrated under vacuum, to afford the title compound which was dissolved in D_2O and analyzed by NMR spectroscopy: ^{1}H-NMR (D_2O): δ 6.95 (d, $J = 520$ Hz, 1 H), 5.7–6.9 (m, 3 H); ^{13}C-NMR (D_2O): δ 137.7 (d, $J_{PC} = 120$ Hz), 131.1 (d, $J_{PCC} = 26$ Hz); ^{31}P-NMR (C_6H_6–THF 4/1) δ 12.2 (dm, $J = 494$ Hz).

Other compounds were characterized as the crude salt: *triethylammonium-cis-prop-1-enyl-phosphinate* [22] *in concentrated reaction mixture*. ^{1}H-NMR (D_2O): δ 6.88 (d, $J = 516$ Hz, 1 H), 6.1–6.4 (m, 1 H), 5.5–5.8 (m, 1 H), 1.69 (br, 3 H); ^{13}C-NMR (D_2O): δ 146.0 (d, $J_{PCC} = 7$ Hz), 130.2 (d, $J_{PC} = 127$ Hz), 22.0 (d, $J_{PCCC} = 21$ Hz); ^{31}P-NMR (D_2O): δ 21.9 (dm, $J = 516$ Hz).

Triethylammonium-trans-prop-1-enyl-phosphinate [22] *salt in concentrated reaction mixture*. ^{1}H-NMR (D_2O): δ 6.87 (d, $J = 514$ Hz, 1 H), 6.1–6.3 (m, 1 H), 5.6–5.7 (m, 1 H), 1.67 (d, $J = 7$ Hz, 3 H); ^{13}C-NMR (D_2O): δ 145.8 (d, $J_{PCC} = 7$ Hz), 130.7 (d, $J_{PC} = 124$ Hz), 22.3 (d, $J_{PCC} = 21$ Hz); ^{31}P-NMR (D_2O): δ 20.9 (dm, $J = 513$ Hz).

4.6. Preparation of 4-hydroxyphosphinoyl-3,6-dihydro-2H-pyridine-1-carboxylic acid-tert-butyl ester (6, Scheme 2)

A solution of *tert*-butyl-1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate (**5**) (0.304 g, 1 mmol), anilinium hypophosphite (**1**) (0.318 g, 2 mmol), anhydrous Et_3N (0.42 ml, 3 mmol), palladium acetate (4.5 mg, 0.02 mmol), and dppp (9.9 mg, 0.024 mmol) in reagent grade C_6H_6 (5 ml) was heated at reflux for 6 h. The reaction mixture was concentrated under vacuum, diluted in water, washed with Et_2O, and loaded on a pad of activated Dowex-50W (pre-washed with MeOH, 3 M HCl, and 5–6 times with distilled water until the eluent was neutral). The pad was eluted with distilled water and $CHCl_3$. The organic layer was separated from the aq. layer, dried over $MgSO_4$, filtered, and concentrated under vacuum to afford the crude title compound in 64% isolated yield: ^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 12.2–12.4 (br, 1 H), 7.08 (d, $J = 562$ Hz, 1 H), 6.57 (d, $J = 23$ Hz, 1 H), 4.05 (br, 2 H), 3.52 (t, $J = 5$ Hz, 2 H), 2.31 (br, 2 H), 1.47 (s, 9 H); ^{13}C-NMR ($CDCl_3$): δ 154.5, 138.1 (br), 129.6 (d, $J_{PC} = 132$ Hz), 80.3, 43.7 (br), 39.4 (br), 28.1 (3 C), 22.8 (d, $J_{PCC} = 11$ Hz); ^{31}P-NMR ($CDCl_3$): δ 24.3 (d, $J = 562$ Hz).

4.7. Preparation of TPMPA (2a, Scheme 2)

To a solution of 4-hydroxyphosphinoyl-3,6-dihydro-2*H*-pyridine-1-carboxylic acid-*tert*-butyl ester (**6**) (0.239 g, 1 mmol) in CH_2Cl_2 (5 ml) was added at −78 °C DBU (0.913 g, 0.90 ml, 6 mmol), MeI (1.419 g, 0.62 ml, 10 mmol), and Me_3SiCl (0.652 g, 0.76 ml, 6 mmol). The reaction mixture warmed to 23 °C overnight, and was concentrated under high vacuum. The crude was dissolved in EtOAc (5 ml), and 3 M HCl (5 ml) was added. The reaction mixture was stirred at 23 °C overnight, concentrated under high vacuum, diluted in water, and loaded on a pad of activated Dowex-50W (pre-washed with MeOH, 3 M HCl, and 5–6 times with distilled water until the eluent was neutral). The pad was eluted with distilled water (50 ml) and $CHCl_3$ (50 ml), and then with a 1:50–1:20 mixture of 12 M NH_4OH and distilled water. The early ninhydrin-negative fractions were rejected, and the later ninhydrin-positive fractions were collected and concentrated under vacuum to afford **2a** in 60% isolated yield. The trace of the side-product (1,2,3,6-tetrahydro-pyridin-4-yl)-phosphonic acid (**2c**) was precipitated by adding EtOH to an aq. solution of the crude. Concentration of the filtrate under vacuum gave the pure title compound: ^{1}H-NMR (D_2O): δ 6.25 (dt, $J = 18$ Hz, $J = 2$ Hz, 1 H), 3.7–3.8 (br, 2 H), 3.32 (t, $J = 6$ Hz, 2 H), 2.45–2.5 (br, 2 H), 1.25 (d, $J = 14$ Hz, 3 H); ^{13}C-NMR (D_2O): δ 140.9 (d, $J_{PC} = 120$ Hz, weak signal), 129.3 (d, $J_{PCC} = 9$ Hz), 44.6 (d, $J_{PCCC} = 14$ Hz), 43.1 (d, $J_{PCCC} = 8$ Hz), 23.6 (d, $J_{PCC} = 9$ Hz), 17.2 (d, $J_{PC} = 98$ Hz); ^{31}P-NMR (D_2O): δ 33.8.

4.8. (1,2,3,6-Tetrahydro-pyridin-4-yl)-phosphinic acid (3, Scheme 2)

Intermediate **6** was hydrolyzed and worked-up as above. ^{1}H-NMR (D_2O): δ 6.90 (d, $J = 531$ Hz, 1 H), 6.23 (d, $J = 23$ Hz, 1 H), 3.71 (s, 2 H), 3.2–3.35 (m, 2 H), 2.4–2.5 (m, 2 H); ^{13}C-NMR (D_2O): δ 137.8 (d, $J_{PC} = 122$ Hz), 130.0 (d, $J_{PCC} = 14$ Hz), 44.6 (d, $J_{PCCC} = 17$ Hz), 42.9 (d, $J_{PCCC} = 9$ Hz), 22.2 (d, $J_{PCC} = 11$ Hz); ^{31}P-NMR (D_2O): δ 22.3 (dd, $J = 533$, 23 Hz).

4.9. trans-Oct-1-enyl-phosphinic acid [5]

^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 10.64 (br, 1 H), 7.2 (d, $J = 562$ Hz, 1 H), 6.6–6.8 (m, 1 H), 5.82 (dd, $J = 17$ Hz, $J = 24$ Hz, 1 H), 2.2–2.3 (m, 2 H), 1.4–1.5 (m, 2 H), 1.2–1.4 (m, 6 H), 0.88 (d, $J = 6$ Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 153.7 (d, $J_{PCC} = 6$ Hz), 120.5 (d, $J_{PC} = 134$

Hz), 34.1 (d, $J_{PCCC} = 20$ Hz), 31.5, 28.7, 27.6, 22.5, 14.0; ^{31}P-NMR ($CDCl_3$): 23.9 (d, $J = 562$ Hz).

4.10. *trans*-Styryl-phosphinic acid [23]

^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 12.28 (br, 1 H), 7.39 (d, $J = 570$ Hz, 1 H), 7.2–7.6 (m, 5 H), 6.3–6.5 (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 148.4 (d, $J = 7$ Hz), 130.4, 128.8 (2 C), 128.6 (d, $J_{PCC} = 19$ Hz), 127.8 (2 C), 117.3 (d, $J_{PC} = 136$ Hz); ^{31}P-NMR ($CDCl_3$): δ 23.5 (dt, $J = 570$ Hz, $J = 23$ Hz).

4.11. (1-Hexyl-vinyl)-phosphinic acid

^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 12.78 (br, 1 H), 7.15 (d, $J = 557$ Hz, 1 H), 5.92 (d, $J = 25$ Hz, 1 H), 5.79 (d, $J = 49$ Hz, 1 H), 2.30 (m, 2 H), 1.5–1.6 (m, 2 H), 1.2–1.4 (m, 6 H), 0.88 (t, $J = 7$ Hz, 3 H); ^{13}C-NMR ($CDCl_3$): δ 142.6 (d, $J_{PC} = 121$ Hz), 127.4 (d, $J_{PCC} = 14$ Hz), 31.46, 30.5 (d, $J_{PCC} = 13$ Hz), 28.7, 27.7 (d, $J_{PCCC} = 5$ Hz), 22.5, 13.9; ^{31}P-NMR ($CDCl_3$): δ 27.4 (dm, $J = 557$ Hz).

4.12. (1,2-Dimethyl-propenyl)-phosphinic acid

^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 10.60 (br, 1 H), 7.44 (d, $J = 555$ Hz, 1 H), 2.04 (s, 3 H), 1.83 (s, 6 H); ^{13}C-NMR ($CDCl_3$): δ 149.0 (d, $J_{PCC} = 12$ Hz), 120.6 (d, $J_{PC} = 135$ Hz), 22.0 (d, $J_{PCCC} = 15$ Hz), 21.4 (d, $J_{PCCC} = 13$ Hz), 12.8 (d, $J_{PCC} = 6$ Hz); ^{31}P-NMR ($CDCl_3$): δ 26.1 (d, $J = 555$ Hz).

4.13. (2-Methyl-propenyl)-phosphinic acid

^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 10.0 (br, 1 H), 7.37 (d, $J = 557$ Hz, 1 H), 5.50 (d, $J = 18$ Hz, 1 H), 2.02 (s, 3 H), 1.91 (s, 3 H); ^{13}C-NMR ($CDCl_3$): δ 159.3 (d, $J_{PCC} = 6$ Hz), 116.5 (d, $J_{PC} = 137$ Hz), 28.2 (d, $J_{PCCC} = 20$ Hz), 21.2 (d, $J_{PCCC} = 10$ Hz); ^{31}P-NMR ($CDCl_3$): δ 20.8 (dd, $J = 557$ Hz, $J = 18$ Hz).

4.14. Cyclohex-1-enyl-phosphinic acid

^{1}H-NMR ($CDCl_3$, $SiMe_4$): δ 10.2–10.5 (br, 1 H), 7.05 (d, $J = 572$ Hz, 1 H), 6.72 (d, $J = 25$ Hz, 1 H), 2.17 (br, 4 H), 1.64 (br, 4 H); ^{13}C-NMR ($CDCl_3$): δ 144.9 (d, $J_{PCC} = 13$ Hz), 128.6 (d, $J_{PC} = 133$ Hz), 25.9 (d, $J_{PCC} = 18$ Hz), 22.1 (d, $J_{PCCC} = 12$ Hz), 21.4 (d, $J_{PCCC} = 10$ Hz), 21.1; ^{31}P-NMR ($CDCl_3$): δ 30.1 (d, $J = 572$ Hz).

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