Tetrahedron Letters 50 (2009) 7314–7317

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of phosphonate derivatives of 2,3-dihydroindene

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ARTICLE INFO

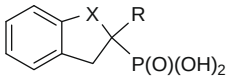
Article history:
Received 29 July 2009
Revised 30 September 2009
Accepted 9 October 2009
Available online 14 October 2009

ABSTRACT

Simple and convenient procedures for the synthesis of derivatives of 2,3-dihydroinden-2-ylphosphonic acid are developed. The reaction strategies utilize both functionalization of the already existing 2,3-dihydroindene skeleton and an annulation reaction starting from readily available *o*-disubstituted benzene derivatives.

Compounds based on the 2,3-dihydroindene skeleton are important in medicine as agents for the treatment of anoxemic and hypoxic symptoms and accompanying syndromes. They are also used as cerebral activators and as drugs for treating amnesia and presbyophrenia curvative therapy. Furthermore, indene derivatives are potential medicaments for breathing arrest, agents for hypoxia accompanied with KCN poisoning[1] and anti-inflammatories.[2,3] Representatives of these compounds have been applied as neuroactive dopamine β-hydroxylase inhibitors or calcium channel modulators.[4,5] Moreover, the antibacterial properties of this class of compounds have also been reported.[6] This wide variety of physiological responses makes the synthesis of structurally related compounds desirable.

The most common synthetic routes for the preparation of simple systems based on the dihydroindene skeleton involve functionalization of commercially available 2,3-dihydroindene derivatives, or by addition reactions to the double bond of indene proceeding through ionic or radical mechanisms. However, when indene cannot be used, the creation of a new five-membered ring is required.[7–9] Several useful procedures have been published including tandem S_N2 Michael addition,[10] intramolecular Friedel–Crafts alkylation,[11] Friedel–Crafts acylation,[3] or dehydration–cyclization of 3-phenylpropanol derivatives on heating in polyphosphoric acid.[12] Furthermore, [2+2+2] addition reactions using acyclic substrates in the presence of $CpCo(CN)_2$ or Wilkinson's catalyst leading to 2,2-disubstitued derivatives of 2,3-dihydroindene have been reported.[13–15] Additionally, there is a possibility to obtain analogues of natural products bearing a 2,3-dihydroindene moiety via acid-catalyzed cyclodimerization of styrenes.[16] Interestingly, among various reports on the preparation of derivatives of 2,3-dihydroindene, there are only a few papers describing the syntheses of phosphonates based on this bicyclic system.[17–19] Taking into account the fact that these compounds, especially in free acidic form, are expected to possess interesting complexing, biological, and medicinal properties, we report herein our efforts to obtain a series of phosphonic 2,3-dihydroindene derivatives of the general formula:



X= CH_2, C=O
R= H, CO_2H, CO_2Et

Initial attempts were focused on elaboration of the procedure for the synthesis of 2,3-dihydro-1*H*-inden-2-ylphosphonic acid. This compound was obtained by the reaction of indene with phosphorus acid (H_3PO_3) via a free radical addition.[9] However, this approach had several limitations including the necessity of using an initiator, elevated temperature, and long-term exposure to light.[9]

In order to avoid the above inconveniences, the Arbuzov reaction was chosen as a simple method to create a new C–P bond. The substrate, 2-bromo-2,3-dihydroindene **1**, was obtained by reaction of 2-indanol with bromine and triphenylphosphine at low temperature[20] (Scheme 1). Next, compound **1** was refluxed with 20% molar excess of triethyl phosphite in dichloromethane. Unfortunately, the reaction failed even after prolonged reaction times and the use of elevated temperature (up to 180 °C), which presumably results from the very low reactivity of the secondary cycloalkyl bromide in the Arbuzov reaction. The above failure required the introduction of a nucleophilic center at C-2 to enable electrophilic attack of a suitable phosphorus reagent.

Indeed, conversion of the bromide **1** into organomagnesium compound **2** provided a straightforward access to the desired ester **3** via reaction with diethyl chlorophosphite followed by oxidation with dilute aqueous hydrogen peroxide. The resulting product **3** was hydrolyzed using an aqueous solution of hydrochloric acid to yield the desired 2,3-dihydro-1*H*-inden-2-ylphosphonic acid **4**.[21]

The phosphonates **3** and **4** proved to be inconvenient substrates in further reactions. Thus, a strategy exploiting a CH-acid with subsequent five-membered ring-closure seemed to be more appropriate for the introduction of a carboxylic moiety at position 2 of the

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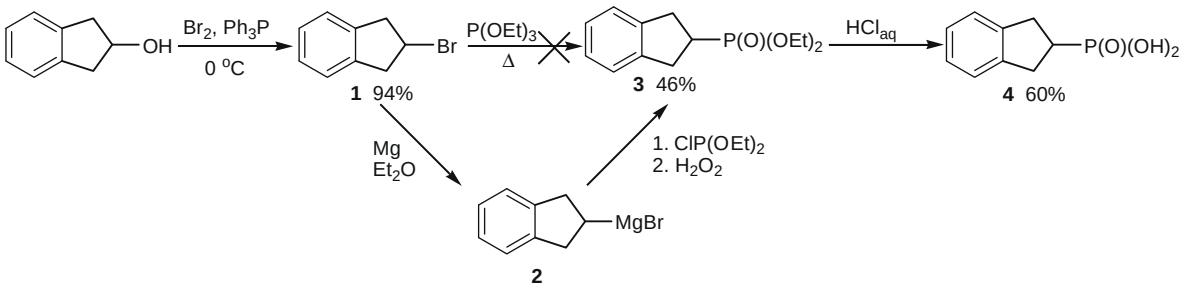
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.042

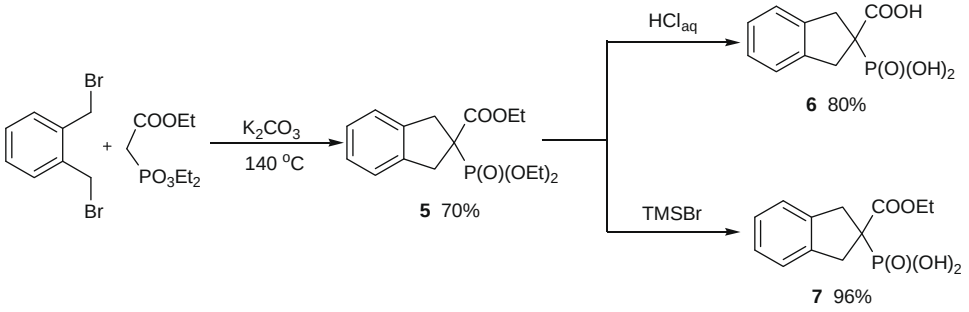


Scheme 1. Synthesis of compound **4**.

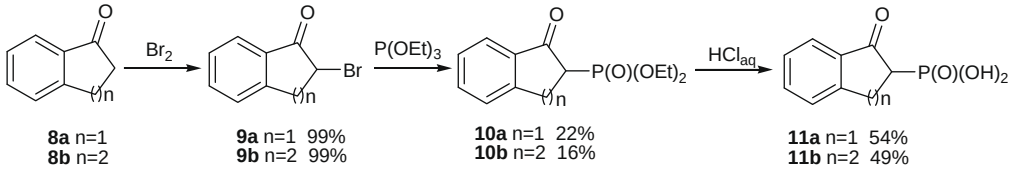
phosphonic acid **4**. Therefore, treatment of 1,2-bis(bromomethyl)benzene with triethyl phosphonoacetate in the presence of a base resulted in the generation of an anion which reacted with the dibromide to yield annulated product **5** (Scheme 2). The best yield was obtained on heating an equimolar amount of substrates with potassium carbonate at 140 °C without solvent. The desired triethyl ester **5** of 2-phosphono-2,3-dihydro-1*H*-indene-2-carboxylic acid was thus formed in a satisfactory yield.

Hydrolysis of **5** was carried out under mild conditions using bromotrimethylsilane (TMSBr) in order to avoid decarboxylation. However, it soon became clear that this approach was only suitable for phosphonate deprotection giving derivative **7** while the ethoxycarbonyl group remained intact.[22] On the other hand, refluxing compound **5** in dilute hydrochloric acid afforded compound **6**. This indicated that the ethyl carboxylate group was highly resistant to decarboxylation, but not to hydrolysis under such conditions.

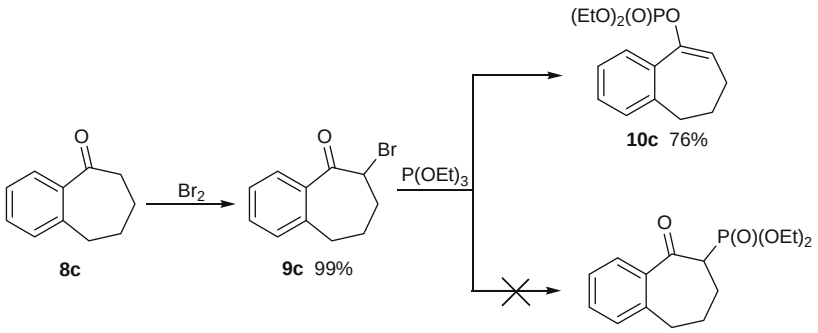
A similar synthetic strategy was employed in an attempt to obtain bisphosphonate analogs utilizing tetraethyl methylenebisphosphonate as an active methylene compound. However, in this case the reaction failed, most likely because the substrate is a weaker CH-acid than phosphonoacetate. The product was not formed irrespective of the reaction conditions and despite the application of strong



Scheme 2. The synthesis of compounds **5**, **6** and **7**.



Scheme 3. A general synthetic route to compounds **11a** and **11b**.



Scheme 4. The synthesis of side-product **10c**.

bases such as sodium *t*-butoxylate, sodium ethoxylate, or sodium hydride.

Finally, we undertook studies on the synthesis of 1-oxo-2,3-dihydro-1*H*-inden-2-ylphosphonic acid **11a** (Scheme 3).[23] Since the preparation of β-ketophosphonates relying on electrophilic phosphorus reagents via Arbuzov reaction is still an attractive approach we intended to prepare the desired compound utilizing this strategy. Thus, 2-bromo-1-indanone **9a** was obtained almost quantitatively by bromination of 1-indanone **8a**. Treatment of **9a** with triethyl phosphite and subsequent hydrolysis gave phosphonic acid **11a**. Extension of this reaction to the preparation of higher homologues of **11a** was also studied. When α-tetralone **8b** was used as substrate the same sequence of reactions gave the desired product **11b**, but in a decreased overall yield. This was due to the formation of vinyl phosphate as a side-product of the Perkov reaction, which is competitive with the Arbuzov reaction. This was even more apparent when 1-benzosuberone **8c** was used as the starting compound. The process resulted in the undesired vinyl phosphate **10c** as the sole product (Scheme 4).

Various modifications in order to counteract side-product formation were thus applied. Attempts involving either protection of the carbonyl group (ketal, hydrazone or oxime) or replacement of bromine with iodine[24,25] were unsuccessful. This is presumably due to stabilization of the intermediate of the phosphate–phosphonate rearrangement by conjugation with the benzene ring. This assumption is based on the literature data, which indicates that vinyl phosphates rearrange smoothly to β-ketophosphonates on reaction with LDA as a result of intramolecular 1,3-migration of phosphorus from oxygen to a carbon atom.[26] This is the reverse reaction to that observed in the case of the benzosuberone derivative.

Summing up, we have presented simple procedures for the preparation of various derivatives of 2,3-dihydro-1*H*-inden-2-ylphosphonic acid. These procedures might be easily modified and applied to the preparation of a wider range of structurally similar compounds.

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21. *2,3-Dihydro-1H-inden-2-ylphosphonic acid* **4**:
To 5.0 g (37.6 mmol) of 2-indanone dissolved in 20 ml of MeOH, 0.54 g (14.3 mmol) of $NaBH_4$ in 20 ml of MeOH was added dropwise. The reaction was stirred vigorously for 2 h at rt. The solvent was evaporated under reduced pressure, the residue was mixed with distilled H_2O and the product was extracted with $CHCl_3$. After drying over anhydrous Na_2SO_4 and removal of the solvent, the crude indanol was crystallized from hexane (3.16 g, yield 63%, mp 67–68 °C, lit. 68–69 °C[27]).
2-Indanol (3.0 g, 22.0 mmol) and 6.15 g (23.0 mmol) of PPh_3 were dissolved in dry CH_2Cl_2 (20 ml) and cooled in an ice bath. To this solution, 1.2 ml (3.7 g, 23.0 mmol) of Br_2 was added dropwise over a period of 0.5 h and then stirring was continued for 2 h at rt. Next, the mixture was poured onto 100 ml of cooled Et_2O. The solid triphenylphosphine oxide was filtered off and the resulting solution was concentrated. The crude bromo derivative was purified by column chromatography (silica/hexane) (4.08 g, yield 94%, colorless oil).
In a two-neck round-bottomed flask equipped with a condenser and dropping funnel, Mg shavings (0.32 g, 13.0 mmol), dry Et_2O (50 ml), and a crystal of I_2 were placed. After 10 min as needed to start the reaction, 2.50 g (13.0 mmol) of 2-bromo-2,3-dihydroindene dissolved in dry Et_2O (5.0 ml) was added dropwise while simultaneously heating the flask. When all the substrate had been added the reaction was continued until the Mg had dissolved. Next, the flask was cooled in an ice bath and a solution of $ClP(OEt)_2$ (2.03 g, 13.0 mmol) in Et_2O (5.0 ml) was added dropwise. The mixture was then stirred for an additional 24 h. A 30% solution of H_2O_2 (5.0 ml) was added to the flask and the mixture was poured onto water (100 ml) and acidified with HCl (2 ml). The crude product was extracted with CH_2Cl_2 and purified by column chromatography (silica/Et_2O) yielding the desired ester as a pale yellow oil (1.5 g, yield 46%). The resulting ester was hydrolyzed by refluxing in HCl (20%, 20 ml) for 4 h. After completion of the reaction the volatile components were evaporated and the crude phosphonic acid **4** was crystallized from hot H_2O (0.55 g, yield 60%, mp 194–195 °C, lit. 196 °C,[28] 195–196 °C[9]).
^{1}H NMR (300 MHz, D_2O): δ 2.57–2.80 (m, 1H), 3.10–3.22 (m, 4H), 7.08–7.14 (m, 2H), 7.14–7.21 (m, 2H). ^{13}C NMR (75 MHz, D_2O): 34.26, 35.82 (d, J_{P-C} = 143.8 Hz), 124.69, 126.75, 142.67 (d, J_{P-C} = 11.8 Hz). ^{31}P NMR (121 MHz, D_2O): δ 31.5. ESI MS *m/z*: 197 $[M-H^+]^-$, 395 $[M_2-H^+]^-$.
22. *Triethyl ester of 2-phosphono-2,3-dihydro-1H-indene-2-carboxylic acid* **5**:
1,2-Bis(bromomethyl)benzene (2.64 g, 10.0 mmol), 4.14 g (30 mmol) of anhydrous K_2CO_3, and 2.24 g (10.0 mmol) of triethyl phosphonoacetate were placed in a round-bottomed flask and heated at 140 °C for 6 h. The crude ester was then extracted with CH_2Cl_2 and purified by column chromatography (silica/Et_2O) yielding 2.28 g (70%) of pure product **5**.
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.1 Hz), 1.28 (t, 6H, *J* = 7.1 Hz), 3.57 (dd, 2H, *J* = 16.4 Hz, *J* = 18.3 Hz), 3.71 (dd, 2H, *J* = 9.6 Hz, *J* = 16.9 Hz), 4.05–4.24 (m, 6H), 7.11–7.23 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.04, 16.32 (d, *J* = 3.9 Hz), 54.60 (d, *J* = 138.1 Hz), 61.92, 63.00 (d, J_{P-C} = 6.2 Hz), 124.11, 126.81, 140.00 (d, J_{P-C} = 9.3 Hz), 171.40. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.76
ESI MS *m/z*: 675 $[2M+Na^+]^+$, 349 $[M+Na^+]^+$, 253 $[M-COOC_2H_5]^+$, 225 $[M-COOC_2H_5-C_2H_5+H^+]^+$.
Ethyl ester of 2-phosphono-2,3-dihydro-1H-indene-2-carboxylic acid **7**:
Ester **5** (0.67 g, 2.0 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and 1.05 ml (1.22 g, 8.0 mmol) of TMSBr was added dropwise. The solution was stirred at room temperature for 24 h. The solvent was removed on a rotary evaporator, MeOH (10 ml) was added and the mixture was stirred for 1 h followed by evaporation of the solvent under reduced pressure. The residue was washed with MeOH, then with Et_2O and dried. Pure product **7** was obtained as an amorphous solid (0.52 g, 96%, 61–62 °C).
^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 (t, 3H, *J* = 7.2 Hz), 3.38 (dd, 2H, *J* = 16.5 Hz, *J* = 18.8 Hz), 3.56 (dd, 2H, *J* = 7.6 Hz, *J* = 16.5 Hz), 4.04 (q, 2H, *J* = 7.2 Hz), 7.08–7.14 (m, 2H), 7.15–7.22 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 14.89, 55.21, 61.96 (d, J_{P-C} = 132.0 Hz), 125.00, 127.45, 141.68 (d, J_{P-C} = 8.3 Hz), 173.12. ^{31}P NMR (121 MHz, DMSO-d_6): δ 20.75. ESI MS *m/z*: 241 $[M-C_2H_5^+]^-$, 269 $[M-H^+]^-$, 539 $[M_2-H^+]^-$.
2-Phosphono-2,3-dihydro-1H-indene-2-carboxylic acid **6**:
Ester **5** (2.28 g, 7.0 mmol) was refluxed in HCl (20%, 15 ml) for 5 h. The excess HCl was evaporated under reduced pressure and the phosphonic acid was crystallized from a mixture of PhMe and MeOH (1.35 g, yield 80%, 79–81 °C).
^{1}H NMR (300 MHz, D_2O): δ 3.40 (dd, 2H, *J* = 18.5 Hz, *J* = 16.6 Hz), 3.55 (dd, 2H, *J* = 16.6 Hz, *J* = 8.3 Hz), 7.15 (m, 2H), 7.22 (m, 2H). ^{13}C NMR (75 MHz, D_2O): 38.77 (d, J_{P-C} = 2.2 Hz), 54.73 (d, J_{P-C} = 130.4 Hz), 124.28, 126.86, 140.82 (d, J_{P-C} = 7.7 Hz), 177.11. ^{31}P NMR (121 MHz, D_2O): δ 21.25.
ESI MS *m/z*: 197 $[M-COOH]^-$, 241 $[M-H^+]^-$, 483 $[2M-H^+]^-$.
23. *General procedure for the synthesis of β-ketophosphonates*:
To a solution of the appropriate ketone (68.4 mmol) in Et_2O (40 ml), Br_2 (68.4 mmol, 10.8 g, 3.5 ml) was added dropwise whilst cooling in an ice bath. To complete the reaction, the mixture was stirred for an additional 15 min, then poured onto distilled H_2O (100 ml) and the organic phase was separated, washed with 5% $Na_2S_2O_3$, and once more with distilled H_2O. After drying over $MgSO_4$ and evaporation of the solvent, the corresponding bromoketone was obtained almost quantitatively. The resulting products were used in the next step without further purification.
2-Bromoketone (68.0 mmol) was mixed with $P(OEt)_3$ (11.6 g, 12.0 ml, 70 mmol) and heated at 100 °C for 3–7 h (monitoring by TLC). The resulting β-ketophosphonate was isolated by column chromatography (silica/AcOEt). Diethyl 1-oxo-2,3-dihydro-1*H*-inden-2-ylphosphonate **10a** was obtained in 22% yield (4.0 g) and diethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-ylphosphonate **10b** in 16% yield (3.0 g).
To the resulting phosphonic diester (10.0 mmol) a 10% aqueous solution of HCl (30 ml) was added and the mixture was refluxed for 10 h. After cooling, the crude phosphonic acid precipitated and was recrystallized from hot H_2O to yield the pure product as the monohydrate.
1-Oxo-2,3-dihydro-1H-inden-2-ylphosphonic acid monohydrate **11a**:
(1.4 g, 54%, 8.8% overall, mp 184–186 °C).
^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10–3.37 (m, 3H(CH)+(CH_2)), 7.39 (t, 1H, *J* = 7.0 Hz), 7.56–7.66 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 29.33 (d, J_{P-C} =

2.4 Hz), 47.97 (d, J_{P-C} = 129.4 Hz), 123.76, 127.21, 127.91, 135.19, 137.14 (d, J_{P-C} = 2.9 Hz), 154.13 (d, J_{P-C} = 5.1 Hz), 200.99 (d, J_{P-C} = 5.5 Hz). ^{31}P NMR (121 MHz, DMSO-d_6): δ 18.45.
ESI MS *m/z*: 193 $[M-H^+-H_2O]^-$, 211 $[M-H^+]^-$, 423 $[M_2-H^+]^-$.
1-Oxo-1,2,3,4-tetrahydronaphthalen-2-ylphosphonic acid monohydrate **11b**:
(1.1 g, 49%, 6.6% overall, mp: 188–189 °C).
^{1}H NMR (300 MHz, DMSO-d_6): δ 2.14–2.36 (m, 3H(CH_2)+(CHP)), 2.80 (dt, 1H, *J* = 16.7 Hz, *J* = 4.4 Hz), 3.01 (dt, 1H, *J* = 25.8 Hz, *J* = 5.1 Hz), 7.28 (d, 1H, *J* = 7.5 Hz), 7.29 (t, 1H, *J* = 8.0), 7.5 (t, 1H, *J* = 7.6 Hz), 7.82 (d, 1H, *J* = 7.8 Hz).
^{13}C NMR (75 MHz, DMSO-d_6): 24.86 (d, J_{P-C} = 3.8 Hz), 26.79 (d, J_{P-C} = 5.3 Hz), 48.70 (d, J_{P-C} = 123.6 Hz), 126.87, 127.10, 129.38, 132.61 (br s), 133.88, 144.80, 193.86 (d, J_{P-C} = 4.93 Hz). ^{31}P NMR (121 MHz, DMSO-d_6): δ 18.18.
ESI MS *m/z*: 225 $[M-H^+]^-$, 451 $[M_2-H^+]^-$, 207 $[M-H^+-H_2O]^-$.

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