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# Phosphonic acid analogs of diclofenac: an Arbuzov reaction of trimethylphosphite with an *ortho*-quinonoid intermediate

Ben Mugrage,* Clive Diefenbacher, Joe Somers, David T. Parker and Tonia Parker

*Arthritis and Bone Metabolism Chemistry Research Department, Novartis Pharmaceuticals, 556 Morris Ave., Summit, NJ 07901, USA*

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**Abstract**

The phosphonic acid analog of the NSAID Diclofenac was efficiently synthesized via an Arbuzov reaction between 2-(2,6-dichloroanilino)benzyl alcohol and trimethyl phosphite followed by TMSBr promoted dealkylation. Seven related phosphonic acids were synthesized using the same novel acid-catalyzed Arbuzov reaction as the key step. 

*Keywords:* Arbuzov reactions; phosphonic acids and derivatives; quinonoid compounds.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) displaying potent anti-inflammatory, analgesic and anti-pyretic activities.[1] We became interested in the phosphonic acid analog (**10a**) of Diclofenac (Fig. 1) because of the potential of identifying similar biological activities. Analogs of this type have not been reported before.

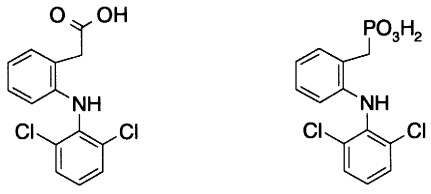


Fig. 1.

To prepare these benzylic phosphonic acids we took advantage of the propensity for benzylic alcohols, bearing an additional heteroatom substituent at the *ortho* or *para* position of the aromatic ring, to ionize under acidic conditions forming resonance stabilized cationic intermediates (**4**), often referred to as quinonoids (Scheme 1).

* Corresponding author.

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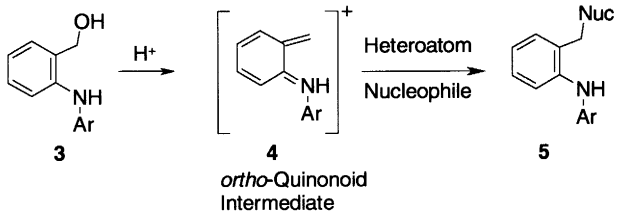
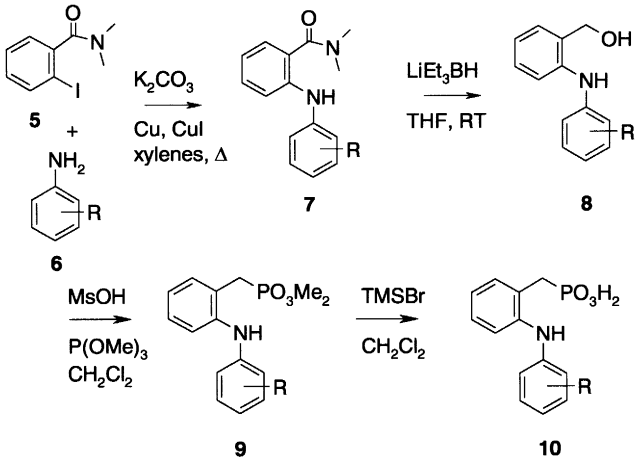



Scheme 1.

Previous reports indicated that *ortho*- and *para*-quinonoid intemediates could be formed from benzylic alcohols under acidic conditions, typically by treatment with zinc iodide. A number of heteroatom nucleophiles including amines,[2] thiols,[3] alcohols[4] and enols[5] have been shown to form a bond at the benzylic position under acidic conditions. Treatment of benzylic alcohols (**8**) with methanesulfonic acid and subsequent capture of the quinonoid intermediates (**4**) with trimethyl phosphite in an Arbuzov[6] reaction resulted in the formation of dimethylphosphonates in good yields. The dimethyl phosphonate products provided an efficient entry to the desired phosphonic acid analogs of Diclofenac (Scheme 2).

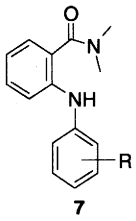



Scheme 2.

The chemistry of Diclofenac has been studied in detail due to its biological significance. A convenient laboratory scale synthetic route[10] uses the Ullmann–Goldberg condensation of 2-iodophenyldimethylactemide with 2,6-dichloroaniline to give the carbon framework for diclofenac.[7] The benzylic alcohol (**8a**) needed for synthesis of the phosphonic acid of diclofenac (**10a**) required the corresponding one carbon lower homolog *N*-anthranilamide.[8] Therefore, as shown in Scheme 2, *N*,*N*-dimethyl-2-iodobenzamide (**5**) was condensed with 2,6-dichloroaniline (**6a**) in the presence of copper and copper(I) iodide to give the expected Ullmann product (**7a**) in good yield. Reduction with lithium triethylborohydride (Super-Hydride®) in THF gave the benzylic alcohol[9] (**8a**) which in turn was stirred with excess (about 20 equiv.) trimethyl phosphite in $CH_2Cl_2$, at room temperature, and treated with 1.5 equiv. of methanesulfonic acid. A slightly exothermic reaction was observed as the benzylic alcohol was completely converted to the dimethylphosphonate (**9a**) in 2 h. Trimethylsilyl bromide promoted dealkylation[11] then gave the phosphonic acid analog (**10a**) in good yield. With other benzylic alcohols (Table 1) the yields of phosphonates varied from 50% to 96% depending on the aniline ring substitution.

Unfortunately, the phosphonic acids did not display the anti-inflammatory biological activity associated with the corresponding carboxylic acid analogs. A cell free system for measuring cyclooxygenase

Table 1
Yields and melting points for dimethyl amides, benzylic alcohol, dimethyl phosphonates and phosphonic acids

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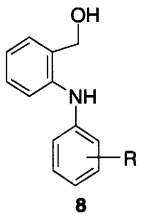


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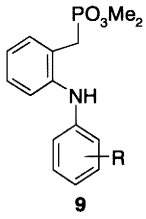


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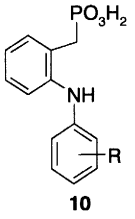


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| Entry | A-Ring Substitution | Dimethylamide yield (mp °C) | Benzyl alcohol yield (mp °C) | Dimethyl phosphonate yield (mp °C) | Phosphonic acid yield (mp °C) |
|---|---|---|---|---|---|
| a | 2,6-diCl | 98% (78-82) | 53% (115-118) | 50% (122-125) | 83% (255-259) |
| b | 2-Me, 3-Cl | 46% (145-148) | 88% (58-61) | 94% (oil) | 53% (225-227) |
| c | 2,4,6-triMe | 50% (oil) | 51% (114-117) | 53% (103-111) | 30% (222-235) |
| d | 2-Me, 3-F | 53% (85-89) | 93% (55-59) | 96% (oil) | 28% (207-209) |
| e | 2,3-diMe | 62% (144-150) | 80% (67-71) | 95% (oil) | 68% (115-120) |
| f | 2,6-diEt, 3-Cl | 58% (oil) | 82% (oil) | 62% (oil) | 72% (223-225) |
| g | 2,6-diEt, 3,5 diCl | 69% (85-87) | 69% (oil) | 86% (oil) | 34% (259-261) |
| h | 2,3,5,6-tetF | 83% (151-153) | 25%* (116-117) | 72% (oil) | 96% (225-226) |

* The corresponding dimethylamine reduction product was obtained in 60% yield.

inhibition was used[12] eliminating the necessity for compounds to cross a lipophilic cell membrane to reach the enzyme. This led to the conclusion that the compounds were inactive at the enzyme level.

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6. (a) As evidence for the formation of the *ortho*-quinonoid we have trapped this intermediate using a 4+2 cycloaddition reaction. The initial report of this work was presented at the 218th ACS National Meeting in New Orleans, Aug. 22–26, 1999, Abstract ORGN490; *Tetrahydroquinolines Generated from Anthranilic Alcohols*; Parker, D. T.; Mugrage, B.; Parker, T. S.; Li, H.; Boehm, C. (b) *Organic Syntheses Based on Named and Unnamed Reactions*; Hassner, A.; Stumer, C.; Pergamon Press: Oxford, 1994; p. 5.
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10. Representative procedures for the conversion of benzylic alcohols to dimethylphosphonates are as follows: **Dimethyl 2-(2′,6′-dichloroanilino)phenylmethylphosphonate (9a)**: Trimethyl phosphite (20 ml, 170 mmol) was added, at rt to a colorless solution of 2-(2′,6′-dichloroanilino)benzyl alcohol (**8a**),(2.38 g, 8.9 mmol) in anhydrous $CH_2Cl_2$ (50 ml). MsOH (0.93 ml, 14 mmol) was added dropwise as a slightly exothermic reaction was observed. After stirring under an inert atmosphere for 2 h, the reaction mixture was diluted with 1:1 $Et_2O$:EtOAc (200 ml), washed with sat. aqueous $NaHCO_3$ (2×50 ml), brine (50 ml), dried over $MgSO_4$, and concentrated on a rotovap. Upon standing the resulting oil crystallized. Trituration with hexanes/$Et_2O$ and filtration gave 1.6 g (50% yield) of an orange solid (mp 122–125°C). H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.31 (d, 1H, J=7.31 Hz), 7.20 (d, 2H, J=7.72 Hz), 7.09 (t, 1H, J=7.72 Hz), 6.98–6.91 (m, 2H), 6.55 (d, 1H, J=6.55 Hz), 3.74 (s, 3H), 3.70 (s, 3H), 3.36 (d, 2H, J=21.33 Hz); P NMR ($CDCl_3$, 300 MHz): $\delta$ 30.88, (s); MS(ESI+): 359.8 *m/e*; IR(KBr): 3250, 1585, 1575, 1452 $cm^{-1}$. **Dimethyl 2-(2′,3′-dimethylanilino)phenylmethylphosphonate (9e)**: Trimethylphosphite (20 ml, 170 mmol) was added, at rt to a solution of 2-(2′,3′-dimethylanilino)benzyl alcohol (**8e**) (2.0 g, 8.8 mmol) in anhydrous $CH_2Cl_2$ (30 ml). MsOH (0.93 ml, 14 mmol) was added dropwise as a slightly exothermic reaction was observed. After stirring under an inert atmosphere for 2 h, the reaction mixture was diluted with 1:1 $Et_2O$:EtOAc (200 ml), washed with sat. aqueous $NaHCO_3$ (2×50 ml), brine (50 ml), dried over $MgSO_4$, and concentrated on a rotovap. The resulting oil was purified by flash chromatography ($SiO_2$, 4:1 EtOAc:hexane) to give 2.8 g (95% yield) of the title phosphonate as a light-yellow oil. H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.26–7.21 (m, 2H), 7.09 (t, 1H, J=7.72 Hz), 6.95 (t, 1H, J=7.72 Hz), 6.85 (t, 1H, J=7.35 Hz), 6.75–6.73 (m, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.32 (d, 2H, J=21.32 Hz), 2.24 (s, 3H), 2.06 (s, 3H); P NMR (DMSO-$d_6$, 300 MHz): $\delta$ 31.49, (s); MS(ESI+): 320.0 *m/e*; IR (thin film):1602, 1583, 1517, 1483, 1473, 1461, 1303, 1232, 1056, 1031, 825 $cm^{-1}$.
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