Simple and Efficient Method for Preparation of Conformationally Constrained Aminomethylene *gem*-Diphosphonate Derivatives *via* Beckmann Rearrangement

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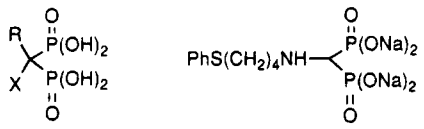
The methylene diphosphonic acids **1**, carbon analogues of inorganic pyrophosphate, exhibit unique physical and chemical properties in interaction with the alkaline earth cations or heavy metal cations.[1] Thus, these compounds are known to possess a number of useful biological properties including antiviral, antiamoebic, herbicidal and "bone-seeking" activities which appear to be related to their ability to chelate metal ions.[2] Recently, aminomethylene *gem*-diphosphonates such as **2** were found to possess inhibitory activity on squalene synthetase, which plays an important role in the pathway of cholesterol biosynthesis, in addition to their inhibitory effects on bone resorption.[3]



1 R=Alkyl, X=OH, NH_2, H **2**

The development of a facile method for the synthesis of alicyclic analogues of aminomethylene *gem*-diphosphopnates would be primary objective for elucidation of structure activity informations on their conformational constraints.[4] Acid catalyzed reactions of nitriles and amides with phosphorous acid or dialkyl phosphites are known to be one of the most useful methods for the synthesis of aminomethylene *gem*-diphosphonic acid derivatives.[5] However, to the best of our knowledge, simple and efficient methods for the synthesis of alicyclic analogues of aminomethylene *gem*-diphosphonates are not available. In this paper we report diphosphonylation reactions of oximes *via* Beckmann rearrangement to give the alicyclic aminomethylene *gem*-diphosphonates efficiently.

Iminocarbocations **5** produced by Beckmann rearrangement of an oxime **3** have been shown to be useful reactive intermediates which react with a variety of C-nucleophiles under the appropriate conditions to give important nitrogen heterocycles after reductive- or alkylative work-up.[6,7] In this context, Beckmann rearrangement of an oxime in the presence of suitable phosphorus nucleophiles would constitute a facile formation of aminomethylene *gem*-diphosphonate **7**, if the phosphorus nucleophiles capture both the intermediate iminocarbocations **5** and the resulting imino phosphonates **6**, effectively under the conditions (Scheme 1).

Therefore, the Beckmann rearrangements of oximes **3a–f** in the presence of representative phosphorus nucleophiles [$(EtO)_3P$ or $HP(O)(OEt)_2$] under the conventional conditions using phosphorus oxychloride ($POCl_3$) as promoter were examined. The results are summarized in Table 1. All reactions gave the expected diphosphonate derivatives **7a–f** in modest yields. In the case of diphosphonylation reactions with cyclic aliphatic oximes such as **3a** and **3b**, $HP(O)(OEt)_2$ was found to be the better phosphorus reagent; when $(EtO)_3P$ was utilized as a phosphorus reagent, a large amount of the corresponding lactams were produced and yields of **7a** and **7b** were low (Table 1, entries 1, 3 *vs* 2, 4). Diphosphonylation reactions of unsymmetrical aromatic oximes such as **3c–f** gave the expected diphosphonates **7c–f** regioselectively with migration of the aromatic groups upon using $(EtO)_3P$ as a phosphorus reagent (Table 1, entries 6–9). The corresponding regioisomers were not detected from these reactions.

All diphosphonate derivatives thus obtained show diagnostic triplets ($J \cong 140$ Hz) at δ 57.8 – 63.6 due to carbons bearing *gem*-diphosphonate groups in their ^{13}C NMR spectra. Structure of **7c, e** was deduced by diagnosis of triplets (δ 1.70 and 1.57; $J \cong 17$ Hz) attributed to the methyl protons α to the diphosphonate groups in their ^1H NMR spectra. Regiochemistry of **7f** derived from tetralone oxime **3f** was unambiguously determined on the basis of the characteristic signal (δ 21.8; t, $J = 8.5$ Hz) corresponding to C(2) methylene carbon in its ^{13}C NMR spectrum.

Oxime mesylate **4c** was also available as a substrate for the diphosphonylation reaction.[8] Treatment of **4c** with Et_2AlCl (1.2 equiv.) in the presence of an excess amount of $(EtO)_3P$ in CH_2Cl_2 at −78 °C, followed by warming to room temperature, gave **7c** in 68% yield (Scheme 2). The yield of **7c** through this method was slightly better than that from oxime **3c** under the conditions described above.

The reaction of **7c** with trimethylsilyl bromide (TMSBr) in CH_2Cl_2, followed by methanolysis gave the corresonding aminomethylene diphosphonic acid **8c** in 59% yield.[9] The results demonstrate that aminomethylene *gem*-

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(6) Reviews on Beckmann rearrangement: Gawley, R. E. *Organic Reaction*, **1986**, *35*, 1.
(7) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. Matsumura, Y.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 6312.
(8) Due to their thermal instability of aliphatic cyclic oxime mesylates **4a,b**, diphosphonylation reactions of **4a,b** under the conditions were found not to be facile.
(9) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M-C. *Tetrahedron Lett.* **1977**, 155.

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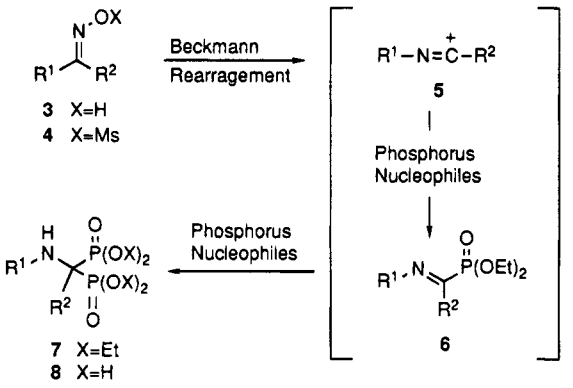
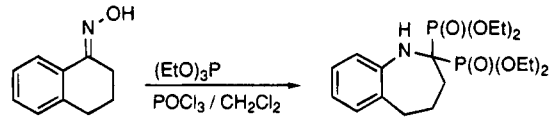
Scheme 1



a: $R^1=R^2=$ -$(CH)_4$-; **b**: $R^1=R^2=$ -$(CH)_5$- ; **c**: $R^1=C_6H_5$, R^2=Me
d: $R^1=C_6H_5$, R^2=Et; **e**: R^1=4-$MeOC_6H_5$, R^2=Me



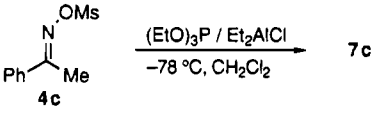
3f 7f

Table 1. Diphosphonylation Reactions of Oximes 3a–f *via* Beckmann Rearrangement Using $POCl_3$ as Promoter

entry[a]	oxime	phosphorus nucleophiles (equiv)	$POCl_3$ (equiv)	time (h)	product	yield[b] (%)
1	**3a**	$(EtO)_3P$ (2.2)	2	2	**7a**	43
2	**3a**	$HP(O)(OEt)_2$ (3.0)	3	4	**7a**	54
3	**3b**	$(EtO)_3P$ (2.2)	2	10	**7b**	43
4	**3b**	$HP(O)(OEt)_2$ (3.0)	3	10	**7b**	55
5	**3c**	$HP(O)(OEt)_2$ (3.0)	3	10	**7c**	43
6	**3c**	$(EtO)_3P$ (2.2)	2	2	**7c**	60
7	**3d**	$(EtO)_3P$ (2.2)	2	10	**7d**	34
8	**3e**	$(EtO)_3P$ (2.2)	2	10	**7e**	44
9	**3f**	$(EtO)_3P$ (3.0)	3	10	**7f**	30

[a] All reactions were carried out in CH_2Cl_2 (0.5 M) at room temperature. [b] Yield refers to isolated pure compounds.

Scheme 2



4c

diphosphonates **7** could be converted to the corresponding acids **8**, required for their biological evaluation, without any difficulty.

Since various methods for the synthesis of substituted analogues of ketones are available, the present reactions should be useful as the method for the preparation of a variety of conformationally constrained aminomethylene *gem*-diphosphonates.

Experimental Section

General. All reactions were carried out under nitrogen. CH_2Cl_2 was distilled from P_2O_5 prior to use. Oximes **3a–f** were prepared from the corresponding ketones by general literature procedure.[6] Oxime mesylates **4** were prepared according to the general procedure of Yamamoto[7] and used without purification. ^{31}P NMR was taken in $CDCl_3$ using 85% H_3PO_4 as external standard with broad-band ^1H decoupling.

Representative Procedure for Preparation of Tetraethyl α-Aminodiphosphonates 7 from Oximes 3. To the solution of an oxime **3** (10 mmol) and the phosphorus nucleophile (22 mmol) in CH_2Cl_2 (20 mL) was added phosphorus oxychloride (3.07 g, 20 mmol) under ice-cooling. The mixture was allowed to warm to room temperature and stirred for several hours as indicated in Table 1. The reaction mixture was made alkaline with 28% NH_4OH and extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude oil. Purification of the oil on silica gel (Et_2O:EtOAc = 1:1) gave the corresponding tetraethyl aminomethylene diphosphonates **7**.

Preparation of Diphosphonate 7c from Oxime Mesylate 4c. To a stirred solution of oxime mesylate **4c**[7] (1.1 g; 5 mmol) and triethyl phosphite (2.1 mL; 10 mmol) in CH_2Cl_2 (10 mL) was added 6 mL of Et_2AlCl (1 M solution in hexane) at −78 °C. The mixture was stirred for 30 min at the same temperature and allowed to stand at 20 °C for 30 min. The reaction was quenched with 28% NH_4OH. The biphasic mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residual oil was purified by silica gel column chromatography to give **7c** in 68% yield.

2,2-Bis(diethylphosphono)piperidine (7a): an oil; ^{13}C NMR ($CDCl_3$) δ 63.2 (with small splits), 62.7 (with small splits), 57.8 (t, $^1J_{PC}$ = 140.8 Hz), 41.7 (t, $^3J_{PC}$ = 6.7 Hz), 25.9, 24.7, 19.8 (t, $^2J_{PC}$ = 6.6 Hz), 16.5; ^{31}P NMR ($CDCl_3$) δ 22.7; IR (neat) 3749, 1240, 1040 cm^{-1}; EIMS *m/z* 357 (M^+), 220 [M^+ − P(O)$(OEt)_2$; 100]. Anal. Calcd for $C_{13}H_{29}NO_6P_2$: C, 43.69; H, 8.18; N, 3.92. Found: C, 43.34; H, 8.20; N, 3.92.

2,2-Bis(diethylphosphono)-2,3,4,5,6,7-hexahydro-2*H*-azepine (7b): an oil; ^{13}C NMR ($CDCl_3$) δ 63.1, 62.9, 61.5 (t, $^1J_{PC}$ = 143.4 Hz), 44.3(t, $^3J_{PC}$ = 6.7 Hz), 33.3, 30.9, 30.4, 23.8 (t, $^2J_{PC}$ = 6.6 Hz), 16.5; ^{31}P NMR ($CDCl_3$) δ 23.4; IR (neat) 3490, 1240, 1040 cm^{-1}; EIMS *m/z* 369 (M^+ − 2), 234 [M^+ − P(O)(O-Et)$_2$]. Anal. Calcd for $C_{14}H_{31}NO_6P_2$: C, 45.28; H, 8.41; N, 3.77. Found: C, 45.58; H, 8.48; N, 3.85.

Tetraethyl 1-methyl-1-anilinomethylenediphosphonate (7c): an oil; ^1H NMR ($CDCl_3$) δ 7.25–7.10 (2H, m), 7.05–6.9 (3H, m), 4.5–4.0 (8H, m), 1.70 (3H, t, J_{PH} = 17.2 Hz), 1.30 (6H, t with small splits, *J* = 7.0 Hz), 1.28 (6H, t with small splits, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 143.7 (t, $^3J_{PC}$ = 5.5 Hz), 128.5, 122.6, 121.9, 63.6 (d, $^2J_{PC}$ = 2.5 Hz), 63.2 (d, $^2J_{PC}$ = 2.7 Hz), 58.5 (t, $^1J_{PC}$ = 146.7 Hz), 16.6 (with small splits), 16.5, 16.4; ^{31}P NMR ($CDCl_3$) δ 21.3; IR (neat) 3480, 1250, 1024 cm^{-1}; MS *m/z* 393 (M^+), 256 [M^+ − P(O)$(OEt)_2$], 199, 118 (100); HRMS calcd for $C_{16}H_{29}NO_6P_2$ *m/z* 393.1470, found 393.1494.

Tetraethyl 1-ethyl-1-anilinomethylenediphosphonate (7d): an oil; ^1H NMR ($CDCl_3$) 7.3–7.0 (3H, m), 6.7 (2H, m), 4.0–4.3 (8H, m), 2.1–2.4 (2H, m); ^{13}C NMR ($CDCl_3$) δ 144.7 (t, $^3J_{PC}$ = 6.1 Hz), 128.6, 120.7, 120.5, 63.2 (t, $^1J_{PC}$ = 143.5 Hz), 63.3(d, $^2J_{PC}$ = 2.9 Hz), 63.2 (d, $^2J_{PC}$ = 3.4 Hz), 24.0, 16.4, 9.0; ^{31}P NMR ($CDCl_3$) δ 22.0; IR (neat) 3479, 1240, 1024 cm^{-1}; EIMS *m/z* 407 (M^+), 270 [M^+ − P(O)$(OEt)_2$], 132 (100); HRMS calcd for $C_{17}H_{31}NO_6P_2$ *m/z* 407.1627, found 407.1648.

Tetraethyl 1-methyl-1-(4-methoxyphenyl)aminomethylenediphosphonate (7e): an oil; ^1H NMR ($CDCl_3$) δ 6.97 (2H, d with small splits, *J* = 8.9 Hz), 6.75 (2H, d with small splits, *J* = 8.9 Hz), 4.4–4.0 (8H, m), 3.76 (3H, s), 1.57 (3H, t, J_{PH} = 17.3 Hz), 1.32 (6H, t, J = 7.0 Hz), 1.30 (6H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 155.8, 136.2 (t, $^3J_{PC}$ = 6.0 Hz), 125.9, 113.6, 63.6, 63.1, 63.1, 58.5 (t, $^1J_{PC}$ = 146.4 Hz), 55.4, 16.4, 16.1; ^{31}P NMR ($CDCl_3$) δ 21.5; IR (neat) 3479, 1510, 1245, 1024 cm^{-1}; EIMS *m/z* 422 (M^+ − 1), 286 [M^+ − P(O)$(OEt)_2$], 149 (100). Anal. Calcd for $C_{17}H_{31}NO_7P_2$: C, 48.22; H, 7.38; N, 3.31. Found: C, 47.92; H, 7.22; N, 3.38.

2,2-Bis(diethylphosphono)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (7f): an oil; ^1H NMR ($CDCl_3$) δ 7.08–7.02 (2H, m), 6.91–6.81 (2H, m), 4.30–4.08 (8H, m), 2.84 (2H, t, *J* = 6.6 Hz), 2.35–2.56 (2H, m), 1.93–1.82 (2H, m), 1.29 (6H, t, *J* = 7.1 Hz), 1.26 (6H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 143.9 (t, $^2J_{PC}$ = 7.14 Hz), 133.3, 129.2, 126.6, 122.3, 121.8, 63.6, 62.8, 61.4 (t, $^1J_{PC}$ = 141.5 Hz), 32.3, 27.9, 21.8 (t, $^2J_{PC}$ = 8.5 Hz), 16.4, 16.3; ^{31}P NMR ($CDCl_3$) δ 21.2; EIMS *m/z* 417 (M^+ − 2), 282 [M^+ − P(O)$(OEt)_2$; 100]; IR (neat) 3419, 1235, 1024 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_6P_2$: C, 51.55; H, 7.45; N, 3.34. Found: C, 50.97; H, 7.38; N, 3.45.

Conversion of Diphosphonate 7c to Phosphonic Acid 8c. Diphosphonate **7c** (1.18 g; 3 mmol) was treated with TMSBr (3.67 g; 24 mmol) in CH_2Cl_2 (6 mL) at 25 °C for 12 h. The

residue, obtained after removal of the solvent, was stirred with MeOH (18 mL) at 25 °C for 2 h and evaporated to give **8c** in 59% yield: mp 208–209 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.14–7.08 (2H, m), 7.02–6.95 (2H, m), 6.81–6.76 (1H, m), 1.60 (3H, t, J_{PH} = 16.2 Hz). Anal. Calcd for $C_8H_{13}NO_6P_2$: C, 34.17; H, 4.66; N, 4.98. Found: C, 33.68; H, 4.58; N, 4.88.

Supplementary Material Available: Photocopies of ^{13}C-NMR and/or ^{1}H-NMR spectra for compounds **7a–f** and **8c** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.