A NOVEL SYNTHESIS OF 1,2-DEHYDRO-1-AMINOPHOSPHONATES *VIA* BECKMANN REARRANGEMENT. APPLICATION TO THE SYNTHESIS OF α-AMINOPHOSPHONIC ACID DERIVATIVES ¶

Tsutomu Yokomatsu, Takayuki Minowa, Yoshinori Yoshida, and Shiroshi Shibuya*

School of Pharmacy, Tokyo University of Pharmacy and Life Science
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

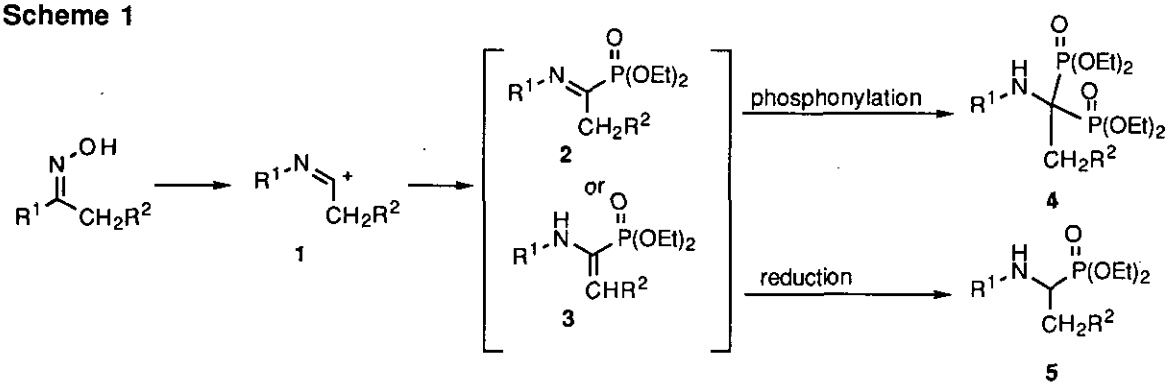
Abstract— Beckmann rearrangement of oxime mesylates (**6a,b** and **6d**) mediated by $TiCl_4$ in the presence of $(EtO)_3P$ gave the 1,2-dehydro-1-aminophosphonates (**7a,b** and **7d**) in good yield. The utility of **7a,b** was illustrated by a synthesis of α-aminophosphonates (**11**) and (**12**).

α-Aminophosponic acids, the phosphonic acid analogs of α-amino carboxylic acids, have received considerable attention over the past decade in medicinal chemistry owing to their potential biological activity and their unique structural features.[1] They have recently proved to be effective components for the synthesis of transition state analog inhibitors for protease.[2] Then, derivatives of α-aminophosphonic acids have been the focus of numerous synthetic studies. Current methodology for construction of these amino acids is available by a variety of routes.[3] The reduction of 1,2-dehydro-1-aminophosphonates are also potentially useful routes for the synthesis of α-aminophosphonic acid derivatives.[4] However, the route for the α-aminophosphonic acid derivatives *via* 1,2-dehydro-1-aminophosphonates has not been extensively studied in part due to a lack of the method of synthesis of 1,2-dehydro-1-aminophosphonic acids derivatives.[4] In this paper, we wish to report that the Beckmann rearrangement of oxime mesylates in the

presence of phosphorus nucleophiles is applicable to a facile synthesis of cyclic 1,2-dehydro-1-aminophosphonates in good yield, in addition to the reductive transformation toward the corresponding α-aminophosphonic acid derivatives.

We have recently reported that the Beckmann rearrangement of oximes in the presence of phosphorus nucleophiles constitutes a facile synthesis of aminomethylene *gem*-diphosphonates (**4**) under the standard conditions ($POCl_3$ / CH_2Cl_2) of Beckmann rearrangement (**Scheme 1**).[5] The intermediate iminocarbocations (**1**) were trapped efficiently with phosphorus nucleophiles to give the iminophosphonates (**2**), these were further phosphonylated to give aminomethylene *gem*-diphosphonate derivatives (**4**). In these reactions, if the phosphonylation process is able to be controlled to isolate the iminophosphonates (**2**) or the synthetic equivalents such as **3**, the subsequent reduction of these intermediates would constitutes a novel synthesis of α-aminophosphonates from oximes *via* Beckmann rearrangement.

Scheme 1

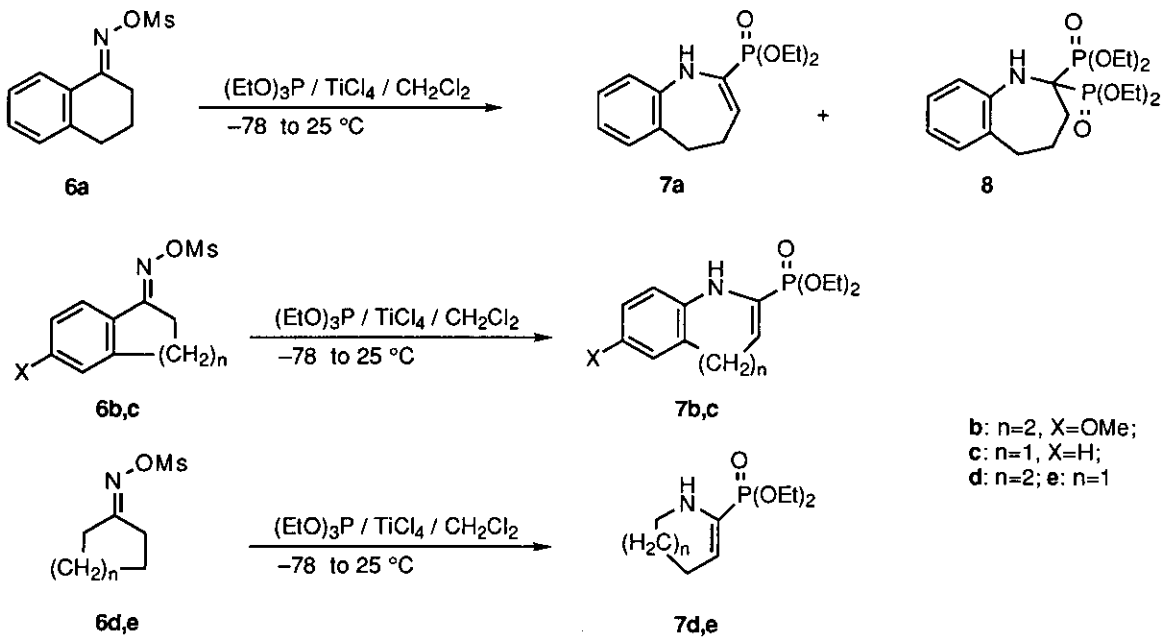


In keeping with this strategy for the synthesis of α-aminophosphonates, Lewis acid-promoted Beckmann rearrangement of oxime mesylates (**6**) of tetralone in the presence of phosphorus reagents was examined under a variety of conditions. Although BF_3•Et_2O and Et_2AlCl did not induce the desired reaction, $TiCl_4$-promoted Beckmann rearrengement of the mesylates (**6**) in the presence of triethyl phosphite $(EtO)_3P$ was found to proceed with the desired mode (**Scheme 2**). Treatment of oxime mesylate (**6a**) with 1.2 equiv. of $TiCl_4$ in the presence of $(EtO)_3P$ (1.2 equiv.) in CH_2Cl_2 at -78 °C for 30 min, followed by warming to 25 °C for 60 min, gave the corresponding 1,2-dehydro-1-aminophosphonate (**7a**) in 62% yield accompanied with a trace of the corresponding aminomethylene *gem*-diphosphonate derivative (**8**).[5,6] The

reaction gave **7a** in virtually the same yield (60%) even in the presence of an excess of $(EtO)_3P$ (3.0 equiv.). 1,2-Dehydro-1-aminophosphonate (**7a**) could be purified by chromatography on silica gel [hexane:EtOAc:Et_3N=80:10:9].

The structure of **7a** was deduced by diagnosis of doublet of triplet (δ 5.56, J=19.4, 4.8 Hz) attributed to the vinyl proton β to the phosphonate in ^1H nmr spectrum.

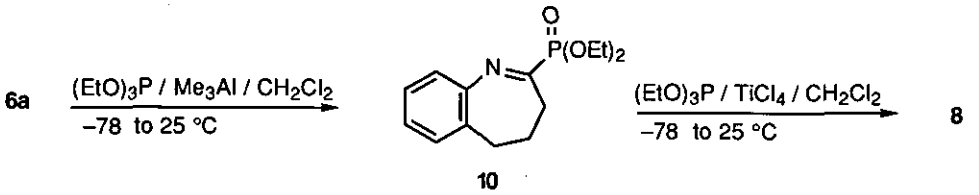
Scheme 2



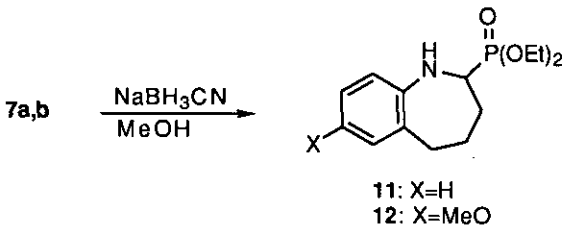
While the Beckmann rearrangement of oxime mesylates (**6c**) and (**6e**) derived from five-membered cycloalkanones such as indanone and cyclopentanone did not give the desired phosphonates (**7c**) and (**7e**), the oxime mesylates (**6b**) and (**6d**) of six-membered cycloalkanones gave the corresponding 1,2-dehydro-1-aminophosphonates (**7b**)[6] and (**7d**)[6] in 55 and 51% yields, respectively, under the same conditions as above.

Formation of **7** might not involve the isomerization of the corresponding iminophosphonates. Because the iminophosphonate (**10**),[7] prepared in low yield (20%) by trimethylaluminum (Me_3Al) catalyzed Beckmann rearrangement of **6a** in the presence of $(EtO)_3P$,[8] gave the aminomethylene *gem*-diphosphonate (**8**)[5] without formation of **7a** upon treatment with $(EtO)_3P$ in the presence of $TiCl_4$. A clear understanding of the

formation of **7** in $TiCl_4$-mediated Beckmann rearrangement of oxime mesylate in the presence of $(EtO)_3P$ must await further experimentation.



1,2-Dehydro-1-aminophosphonates (**7a,b**) thus obtained gave the corresponding α-aminophosphonates (**11**) and (**12**) as oils in good yields [**11**: 84%; **12**: 73%],[6] upon treatment with $NaBH_3CN$ in MeOH containing 2N HCl.[9,10] Thus, $TiCl_4$-catalyzed Beckmann rearrangement of oxime mesylate in the presence of phosphorus reagent constitutes a facile synthesis of α-aminophosphonates *via* reduction of 1,2-dehydro-1-aminophosphonates.



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REFERENCES AND NOTES

¶ Dedicated to professor Shigeru Oae on the occasion of his 77th birthday.

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6. All new compounds except unstable oils provided satisfactory analytical and spectroscopic data. Spectroscopic data of selected new componds: **7a**: an oil; ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.09-7.01 (2H, m), 6.85 (1H, dd, *J*=7.1, 7.5 Hz), 6.75 (1H, d, *J*=7.5 Hz), 5.88 (1H, d, *J*=11.8 Hz), 5.56 (1H, dt, *J*=19.4, 4.8 Hz), 4.20-4.03 (4H, m), 3.02-2.94 (2H, m), 2.63-2.54 (2H, m), 1.40-1.32 (6H, m); ^{13}C nmr (100 MHz, $CDCl_3$) δ 143.96 (d, *J*=13 Hz), 131.37, 130.42, 128.48, 126.68, 121.43, 118.70, 115.18 (d, *J*=12.9 Hz), 62.50 (d, *J*=4.5 Hz), 34.20, 29.77 (d, *J*=16.7 Hz), 16.25 (d, *J*=6.1 Hz); ^{31}P nmr (160 MHz, $CDCl_3$) δ 17.0; ir (neat) 1258, 1235, 1055, 1024 cm^{-1}; ms(EI) *m/z* 281 (M^+); HRms *m/z* calcd for $C_{14}H_{20}NO_3P$: 281.1181, Found: 281.1208. **7b**: an unstable oil; ^{1}H nmr (300 MHz, $CDCl_3$) δ 6.75-6.6 (3H, m), 5.67 (1H, d, *J*=11.7 Hz), 5.48 (1H, dt, *J*=19.0, 5.7 Hz), 4.20-4.05 (4H, m), 3.76 (3H, s), 2.98-2.92 (2H, m), 2.61-2.54 (2H, m), 1.42-1.31 (6H, m); ^{31}P nmr (160 MHz, $CDCl_3$) δ 16.6; ir (neat) 1257, 1234, 1054, 1023 cm^{-1}; ms(EI) *m/z* 295 (M^+). **7d**: an unstable oil, ^{1}H nmr (300 MHz, $CDCl_3$) δ 5.66 (1H, dt, *J*=11.4, 5.83 Hz), 4.20-4.0 (4H, m), 3.85-3.81 (1H, m), 2.39-2.18 (2H, m), 1.75-1.30 (4H, m), 1.38-1.29 (6H, m); ms(EI) *m/z* 233 (M^+); HRms *m/z* calcd for $C_{10}H_{20}NO_3P$: 233.1181, Found: 233.1171. **11**: an oil; ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.10 (1H, d, *J*=6.93 Hz), 7.05 (1H, dd, *J*=7.1, 1.5 Hz), 6.89 (1H, dd, *J*=7.1, 7.5 Hz), 6.85 (1H, d, *J*=7.5 Hz), 4.20-4.10 (4H, m), 3.13 (1H, ddd, *J*=16.1, 11.0, 2.1 Hz), 2.83-2.64 (2H, m), 2.28-2.15 (1H, m), 2.14-1.98 (1H, m), 1.89-1.75 (1H, m), 1.48-1.32 (7H, m); ^{13}C nmr (100 MHz, $CDCl_3$) δ 148.21 (d, *J*=12 Hz), 133.85, 130.55, 126.81, 121.89, 120.28, 62.53 (d, *J*=6.3 Hz), 62.30 (d, *J*=6.6 Hz), 55.50 (d, *J*=144.5 Hz), 35.28, 31.32, 26.36 (d, *J*=16.6 Hz), 16.5 (br s); ^{31}P nmr (160 MHz, $CDCl_3$) δ 27.2; ir (neat) 3329, 1481, 1258, 1228, 1053, 1024 cm^{-1}; ms *m/z* 283 (M^+); HRms *m/z* calcd for $C_{14}H_{22}NO_3P$: 283.1337, Found: 283.1342. **12**: an oil; ^{1}H nmr (300 MHz, $CDCl_3$) δ 6.81 (1H, d, *J*=8.3 Hz), 6.68 (1H, d, *J*=2.8 Hz), 6.61 (1H, dd, *J*=8.3, 2.8 Hz), 4.20-4.10 (4H, m), 3.76 (3H, s), 3.05 (1H, ddd, *J*=16.2, 11.0, 2.1 Hz), 3.39-3.22 (2H, m), 2.25-2.15 (1H, m), 2.09-2.0 (1H, m), 1.90-1.75 (1H, m), 1.39-1.30 (7H, m); ^{13}C nmr (100 MHz, $CDCl_3$) δ 142.50 (d, *J*=12.0 Hz), 136.05, 121.48, 116.16, 111.48, 62.51 (d, *J*=5.9 Hz), 62.31 (d, *J*=6.7 Hz), 55.97 (d, *J*=144.2

Hz), 55.31, 35.42, 31.57, 26.50 (d, J=16.6 Hz), 16.55 (br s); ^{31}P nmr (160 MHz, $CDCl_3$) δ 27.4; ir (neat) 3329, 1505, 1257, 1227, 1051, 1024 cm^{-1}; ms(EI) *m/z* 287 (M^+).

7. Since **10** was difficult to isolate as a pure state due to its instability toward silica gel column chromatography, the structure and yield of **10** were determined after reduction [$NaBH_4$ / MeOH] to α-aminophosphonate (**11**).

8. The competitive methylation of iminocarbocation was the major reaction as reported by Yamamoto: K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.,* 1983, **105**, 2831; Y. Matsumura, J. Fujiwara, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.,* 1983, **105**, 6312.

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10. 1,2-Dehydro-1-aminophosphonates (**7**) were inert to $NaBH_4$-reduction in MeOH. The results also support the structure of **7**.

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