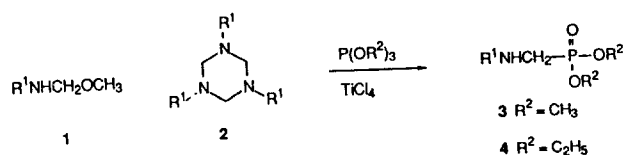


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Scheme 1.

A New Route to N-Substituted Aminomethylphosphonates

Hyun-Joon Ha*, Gong-Sil Nam, and Kyong Pae Park

Division of Chemistry,

Korea Institute of Science and Technology, Seoul 136-791

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Some of N-substituted aminomethylphosphonic acids and their esters are known to have herbicidal and fire-proofing applications.¹ Synthesis of their acids has been developed in a wide variety of methods.^{2,3} However, synthetic methodology of their esters is relatively rare. Only two methods were reported for the preparation of their esters: (1) substitution of chloromethylphosphonates³ or phosphonomethyltriflates⁴ with primary amines (2) rearrangement of P-(halomethyl)-N-phenylphosphonoamides.⁵ These are not generally applicable for diverse N-substituted aminomethylphosphonates.

We recently described that condensation of N-substituted N-methoxymethylamines (1) with trialkylphosphites affords N-substituted aminomethylphosphonates (3,4).⁶ The reaction of N-substituted amine with paraformaldehyde and sodium methoxide in methanol yields either N-substituted N-methoxymethylamine (1) or 1,3,5-trisubstituted-hexahydro-1,3,5-triazine⁷ (2) depending on the substituent R¹.⁸ The heating of 1 under reduced pressure results in a quantitative transformation into the corresponding 2. In this communication we present a new route to the synthesis of 3 and 4 involving the reaction of 2 with trialkylphosphites in the pre-

sence of TiCl₄.⁹ (Scheme 1)

Typical reaction procedure is as follows. To a stirred solution of 1,3,5-trisubstituted-hexahydro-1,3,5-triazine (2) (6 mmol) in 100 ml of CH₂Cl₂ under nitrogen was slowly added TiCl₄ (21 mmol) at 0°C. After being stirred for 10 min, trialkylphosphite (18 mmol) was added. The resulting solution was stirred at 0°C for 1-2 hr. After being observed that all starting material was consumed on TLC the reaction mixture was poured into water. The resulting solution was neutralized with sat. NaHCO₃ solution. The reaction product was extracted with CH₂Cl₂. Organic layer was washed successively with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The reaction product was further purified by column chromatography or short-path distillation. Results are summarized in the Table 1.

This method is widely applicable to the various N-substituted aminomethylphosphonates including simple alkyl (entry 1,2,3), bulky t-butyl (entry 4), allyl (entry 5), cyclohexyl (entry 6,7), phenyl (entry 8), benzyl (entry 9) as substituents. Furthermore, a commercial herbicide N-phosphonomethylglycine¹⁰ is also accessed by this method⁹ as its corresponding trialkylesters (entry 10,11).^{11,12}

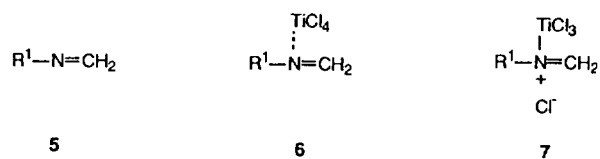
The mechanism of this reaction is not clear. But, α-methyleneamine peaks in ¹H and ¹³C NMR were observed by mixing 1,3,5-trisubstituted-hexahydro-1,3,5-triazine and TiCl₄.¹³ The observed peaks were close to those of free N-substituted methyleneamine¹⁴ generated by flash vacuum thermolysis of the corresponding N-substituted aminoacetonitrile. Moreover, the color of this mixture became deep wine-red, which indicated that formation of α-methyleneamine complex with TiCl₄. On the basis of the observations we predict that this reaction is preceded by

Table 1. N-Substituted Aminomethylphosphonates Prepared from the Reaction of 1,3,5-Trisubstitutedhexahydro-1,3,5-Triazines with Trialkylphosphites in the Presence of Titanium Tetrachloride

Entry	R ¹	R ²	Yield ^{a,b} (%)	¹ H NMR(CDCl ₃) ^c	IR (cm ⁻¹ , P=O)
1	CH ₃ CH ₂	C ₂ H ₅	49	3.16(d, 10 Hz)	1256
2	CH ₃ (CH ₂) ₂ CH ₂	CH ₃	65	3.17(d, 12 Hz)	1249
3	CH ₃ (CH ₂) ₂ CH ₂	C ₂ H ₅	69	3.00(d, 12 Hz)	1239
4	(CH ₃) ₃ C	C ₂ H ₅	45	3.83(dd, 10 Hz, 5 Hz)	1239
5	CH ₂ CHCH ₂	C ₂ H ₅	60	2.94(d, 10 Hz)	1255
6	Cyclo-C ₆ H ₁₁	CH ₃	45	3.06(d, 10 Hz)	1255
7	Cyclo-C ₆ H ₁₁	C ₂ H ₅	48	3.10(d, 10 Hz)	1253
8	Ph	C ₂ H ₅	80	3.54(dd, 12 Hz, 6 Hz)	1212
9	PhCH ₂	C ₂ H ₅	35	3.15(d, 10 Hz)	1257
10	C ₂ H ₅ O ₂ CCH ₂	CH ₃	92	3.17(d, 12 Hz)	1239
11	C ₂ H ₅ O ₂ CCH ₂	C ₂ H ₅	65	3.05(d, 12 Hz)	1238

^aYield of isolated pure product, not optimized except entry 10. ^bSatisfactory microanalyses obtained. ^cChemical shift of two methylene protons between nitrogen and phosphorus, referenced by TMS.

nucleophilic addition of phosphites to α -position of N-substituted methyleneamine (5) or its equivalent (6,7) generated from hexahydro-1,3,5-triazine with TiCl_4 .



Along with the earlier result⁶ N-substituted aminomethylphosphonates can be generally synthesized by the reaction of N-methoxymethylamines or hexahydro-1,3,5-triazines with trialkylphosphites in the presence of TiCl_4 .

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