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R^{1} R^{1} R^{1} R^{1} R^{1} R^{1} R^{1} R^{1} R^{1} R^{2} R^{2

Scheme 1.

A New Route to N-Substituted Aminomethylphosphonates

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Some of N-substituted aminomethylphosphonic acids and their esters are known to have herbicidal and fire-proofing applications. Synthesis of their acids has been developed in a wide variety of methods. However, synthetic methology of their esters is relatively rare. Only two methods were reported for the preparation of their esters: (1) substitution of chloromethylphosphonates or phosphonomethyltriflates with primary amines (2) rearrangement of P-(halomethyl)-N-phenylphosphonoamidates. 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 R^{1,8} 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 tialkylphosphites 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 methods 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-phosphonomethylglycine 10 is also accessed by this method 9 as its corresponding trialkylesters (entry 10,11). 11,12

The mechanism of this reaction is not clear. But, α -methyleneamine peaks in ${}^{1}H$ and ${}^{13}C$ NMR were observed by mixing 1,3,5-trisubstituted-hexahydro-1,3,5-triazine and $\mathrm{TiCl_4}^{13}$. The observed peaks were close to those of free N-substituted methyleneamine 14 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 $\mathrm{TiCl_4}$. On the basis of the observations we predict that this reaction is proceeded 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	phites in the Presence of T	R ²	Yield ^{a,b} (%)	'H NMR(CDCl ₃)'	$IR (cm^{-1}, P = 0)$
	CH ₃ CH ₂	C_2H_5	49	3.16(d, 10 Hz)	1256
l O	CH ₃ (CH ₂) ₂ CH ₂	CH ₃	65	3.17(d, 12 Hz)	1249
2	CH ₃ (CH ₂) ₂ CH ₂	C_2H_5	69	3.00(d, 12 Hz)	1239
3	*	C_2H_5 C_2H_5	45	3.83(dd, 10 Hz, 5 Hz)	1239
4	(CH ₃)C	C_2H_5	60	2.94(d. 10 Hz)	1255
5	CH ₂ CHCH ₂ Cyclo-C ₆ H ₁₃	CH ₃	45	3.06(d, 10 Hz)	1255
6		C_2H_5	48	3.10(d, 10 Hz)	1253
7	Cyclo-C ₆ H ₁₁	C_2H_5	80	3.54(dd, 12 Hz, 6 Hz)	1212
8	Ph	C_2H_5	35	3.15(d. 10 Hz)	1257
9	PhCH ₂	C ₂ 11 ₅ CH ₃	92	3.17(d, 12 Hz)	1239
10 11	$C_2H_5O_2CCH_2 \ C_2H_5O_2CCH_2$	Сл ₃ С ₂ Н ₅	65	3.05(d, 12 Hz)	1238

[&]quot;Yield of isolated pure product, not optimized except entry 10. "Satisfactory microanalyses obtained. Chemical shift of two methylene protons between nitrogen and phosphorus, referenced by TMS.

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

Along with the earlier result⁶ N-substituted aminomethyl-phosphonates 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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