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An Efficient Synthesis of Tertiaryaminomethylphosphonates, A Versatile Precursor for Synthesis of Glyphosate and α-Aminomethylphosphonates

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Abstract: Reaction of simple dialkyl phosphites with symmetrical 1,3,5-trisubstituted hexahydrotriazines (HHTs) in the presence of benzyl chloride, afforded tertiaryaminomethylphosphonates in excellent yields. Glyphosate, α-aminomethylphosphonates and their derivatives can therefore be synthesized by this procedure conveniently.

Keywords: Glyphosate, α-aminomethylphosphonate, 1,3,5-hexahydrotriazine, dialkylphosphite.

Glyphosate, N-(phosphonomethyl)glycine, has achieved great success as a broad spectrum, non-selective herbicide which controls many worst weeds and exhibits very low mammalian toxicity[1]. Accordingly, glyphosate has stimulated a worldwide search for simple and efficient methods for its preparation. Among the versatile approaches, the reaction involves symmetrical 1,3,5-hexahydrotriazine (HHT) following complements Mannich--based procedures seems to be attractive. However, fairly rigorous conditions such as high temperature, and an acid catalyst are needed in reactions between simple aliphatic dialkyl phosphites and HHTs. And no significant product formation was observed in organic solutions, such as toluene or acetonitrile[2] .

In our efforts to synthesize glyphosate triesters[3], we heated dimethyl phosphite with 1,3,5- tricarboethoxy methyl hexahydro-1,3,5-triazine at 100°C under nitrogen for 6 hrs. No desired product was obtained. Surprisingly, in the presence of benzyl chloride, heating the three components at 100°C for 2 hours, afforded ethyl N-benzyl-N- (dimethoxyphosphinylmethyl) glycinate in 92% yield (**Scheme 1**). Benzyl bromide can also be used to produce this compound, with a yield of 81%. Similar results were obtained in 95% ethanol-water solution and dry toluene. Catalytic hydrogenolysis of that glyphosate triester with 5% Pd-C afforded ethyl N-(dimethoxyphosphinylmethyl) glycinate quantitatively.

Tertiaryaminomethylphosphonates **4** can therefore be synthesized conveniently by this procedure (**Table 1**). Catalytic hydrogenolysis of **4** with 5% Pd-C gave the corresponding α-aminomethylphosphonates quantitatively. However, our attempts to synthesize ethyl N- benzyl-N-(dimethoxyphosphinylmethyl) glycinate by reaction of dimethyl phosphite with N- benzyl HHT in the presence of ethyl bromoacetate were

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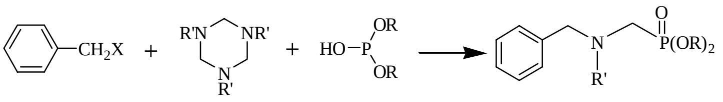
unsuccessful. HHTs were prepared very easily from primary amines and formaldehyde according to the known procedure[4].

Scheme 1



1 **2** **3** **4**

R=CH_3,C_2H_5
R'=$CH_2CO_2C_2H_5$,C_2H_5,benzyl
X=Cl,Br

Table 1 Structures of compounds 4**a-l** and their yields

Entry	R′	X	R	Yield (%)*
a	$CH_2CO_2C_2H_5$	Cl	CH_3	92
b	$CH_2CO_2C_2H_5$	Cl	C_2H_5	92
c	$CH_2CO_2C_2H_5$	Br	CH_3	81
d	$CH_2CO_2C_2H_5$	Br	C_2H_5	80
e	benzyl	Cl	CH_3	91
f	benzyl	Cl	C_2H_5	90
g	benzyl	Br	CH_3	78
h	benzyl	Br	C_2H_5	76
i	C_2H_5	Cl	CH_3	89
j	C_2H_5	Cl	C_2H_5	89
k	C_2H_5	Br	CH_3	75
l	C_2H_5	Br	C_2H_5	75

*Isolated yield based on HHTs.

In summary, we observed an interesting ring-opening reaction of HHTs with simple dialkyl phosphites, and developed it as a versatile and convenient procedure for synthesis of tertiaryaminomethylphosphonates. This HHTs procedure is particularly convenient for laboratory-scale synthesis of glyphosate and a wide variety of its derivatives.

References and Notes

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5. General Procedure for preparation of tertiaryaminomethyphosphonates **4**: A mixture of benzyl chloride (3.78 g, 30 mmol), HHT of ethyl glycinate (3.45 g, 10 mmol), dimethylphosphite (3.30 g, 30 mmol) and 95% ethanol (10 mL) was heated to reflux for 2 hr. After removal of solvent, 20 ml saturated sodium bicarbonate solution was added and the reaction mixture was then thoroughly extracted with ethyl acetate (3×20 mL). The extract was collected and dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent and the residue was purified by chromatography on silica gel, eluting with ethyl acetate and hexane (1:1) to give ethyl N-benzyl-N-(dimethoxyphos- phinyl methyl) glycinate (9.06 g, 92%) as a colorless oil. All the analytical data (IR, NMR and MS *etc)* of tertiaryaminomethylphosphonates **4** were consistent with their structures.

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