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LETTERS

Tetramethylguanidine (TMG)-Catalyzed Addition of Dialkyl Phosphites to α,β–Unsaturated Carbonyl Compounds, Alkenenitriles, Aldehydes, Ketones and Imines

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Abstract: Tetramethylguanidine-catalyzed addition of dialkyl phosphites to α,β-unsaturated carbonyl compounds, alkenenitriles, aldehydes and ketones constitutes a practical route to a variety of phosphonate synthons. The very mild conditions employed, together with the short reaction times, make the procedure highly versatile and tolerant to a range of functionalities. The proposed methodology is also convenient for the preparation of α-aminophosphonates. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Phosphonates are versatile intermediates in organic synthesis primarily due to their application in the Wadsworth-Emmons and related reactions.[1,2] In the last few years, phosphonates have been the focus of intensive studies due to their interest as stable transition state analogue enzyme inhibitors. In fact, the phosphonate and phosphonic acid moieties may be accepted by enzymes as false substrates and interfere with biological processes.[3,4]

Owing to their synthetic and biological values, the chemistry of phosphonates has stimulated an increasing interest and the development of new methodologies for their preparation still remains of great interest.[5-7]

Previous results from our laboratory demonstrated that tetramethylguanidine (TMG) catalyzes the Michael addition of nitromethane to α,β-unsaturated carboxylic acid esters as well as to α,β-unsaturated ketones.[8,9] Recently, we have also demonstrated that the TMG-catalyzed addition of primary nitroalkanes to aldehydes and alicyclic ketones (Scheme 1) constitutes a practical means to perform the nitro-aldol reaction (Henry reaction).[10] Since TMG has been used only sporadically and has not yet received full recognition as a general strong base in organic synthesis, we have been exploring its behaviour towards diverse base-catalyzed reactions. Specifically, we wished to extend its utility to the addition of dialkyl phosphites (P-H bond) to unsaturated systems such as α,β-unsaturated carboxylic acid esters and ketones or saturated aldehydes and ketones (Scheme 2).

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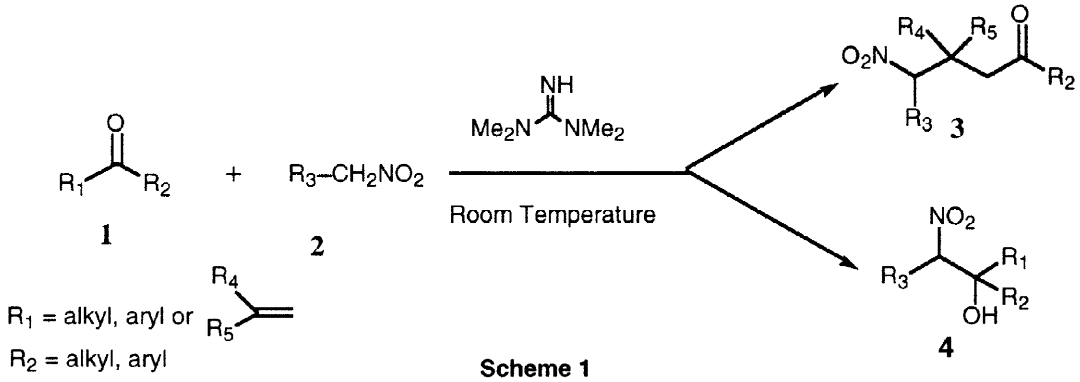
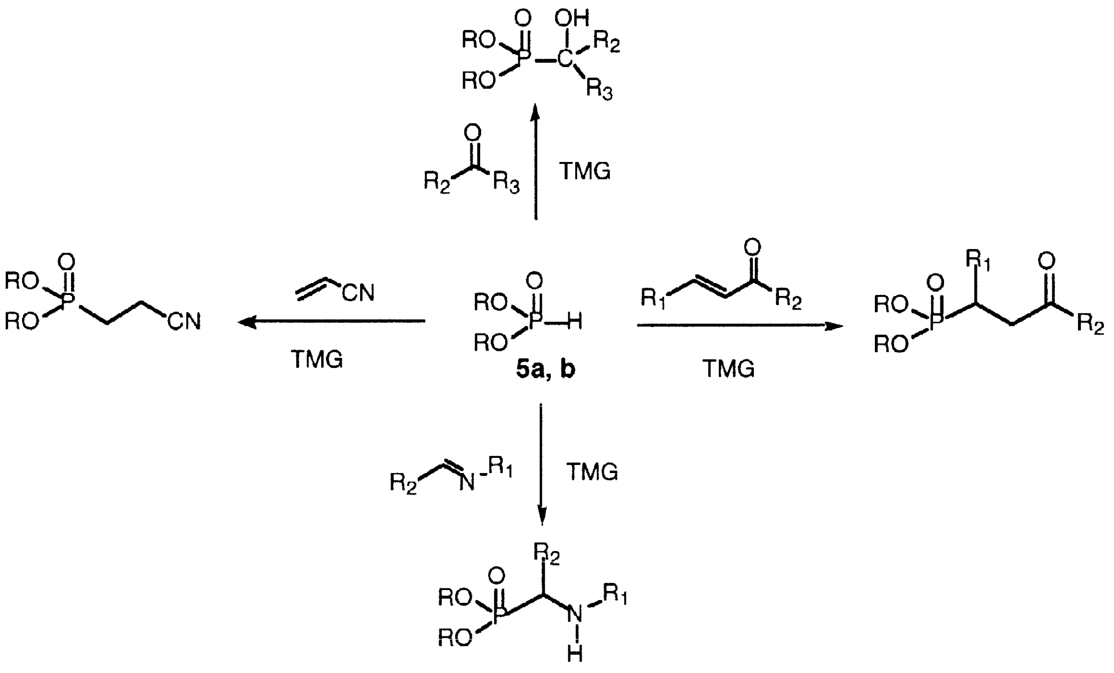
Although these reactions have been reported to occur occasionally in the absence of a catalyst, and the use of aliphatic amines as catalysts has also been described, the addition usually takes place in the presence of alkaline alkoxides in alcoholic solution. Therefore, the use of TMG as the catalyst to perform the addition of dialkyl phosphites to unsaturated systems could offer significant advantages especially in terms of experimental simplicity, milder reaction conditions and easy work-up, and could represent a convenient tool for the synthesis of a variety of phosphonate synthons.



Scheme 1

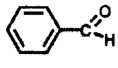
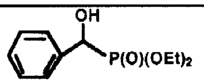
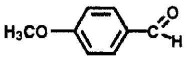
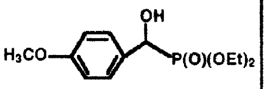
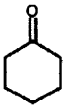
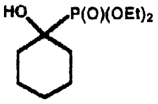
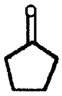
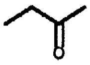
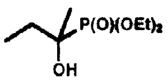
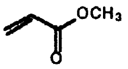
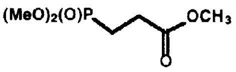
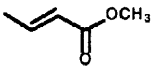
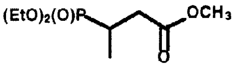
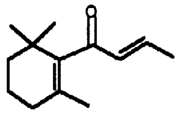
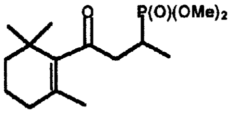
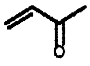
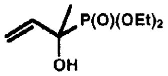
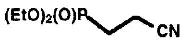
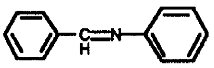
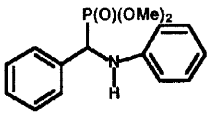
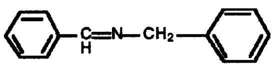
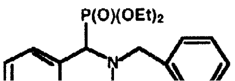
In this letter we report our preliminary results concerning the tetramethylguanidine(TMG)-catalyzed addition of dialkyl phosphites to a variety of α,β-unsaturated compounds including carboxylic acid esters ketones, and nitriles, as well as to saturated aldehydes, ketones and imines .



Scheme 2

The addition reaction takes place smoothly giving rise to the corresponding phosphonates in good yield (Table) on slow addition of the α,β-unsaturated carbonyl compound (1 mmol) to the dialkyl phosphite (5 ml)

Table: Synthesis of Alkyl Phosphonates by TMG-Catalyzed Addition of Phosphites to Unsaturated Systems

Entry	Carbonyl Compd.	Phosphites	Reaction time and Temp.	Product	Yield* %
1		**5a**	12 h 0°C		86
2		**5a**	12 h r.t		60
3		**5a**	12 h r.t.		66
4		**5a**	12 h r.t.		55
5		**5a**	12 h 0°C		78
6		**5b**	1 h 0°C		71
7		**5a**	12 h r.t.		51
8		**5b**	12 h r.t.		88
9		**5a**	2 h 0 °C		54
10		**5a**	1 h 0°C		47
11		**5b**	2 h r.t.		73
12		**5a**	2 h r.t.		81

5a corresponds to diethyl phosphite and **5b** to dimethyl phosphite.
* Purified compounds

containing a catalytic amount of TMG (two drops).The reaction can be applied successfully to all the α,βunsaturated compounds examined (ketones, carboxylic acid esters and nitriles) simply through slight modification of the reaction conditions (see times and temperatures in the Table). In all cases good yields were obtained. Usually, the reaction proceeds smoothly and cleanly under very mild conditions (in many cases the reaction works efficiently at 0°C) and no side reactions were observed. As an exception, methyl vinyl ketone failed to give the Michael adduct, the 1,2-addition product being formed preferentially. Hence, we observed that TMG catalyzes the addition of dialkyl phosphites to aldehydes and ketones at room temperature or 0° C, producing good yields of α-hydroxyphosphonates (see Table). As a general rule, an excess of the dialkyl phosphite and/or of the carbonyl compound may be used; moreover, solid phosphonates may easily be recovered by simple filtration of the reaction mixture.

Having demonstrated that TMG can afford a facile catalyzed addition of dialkyl phosphites to unsaturated systems, we decided to investigate its behaviour towards the addition of phosphites to imines. To this regard, benzylideneaniline reacted easily with dimethyl phosphite to afford the corresponding α-aminophosphonate (entry 11), a compound previously obtained at reflux in ethanol and in the presence of sodium ethoxide.[5]

In conclusion, we have demonstrated the extraordinary ability of TMG to accomplish the addition of phosphites to both saturated and α,β-unsaturated carbonyl compounds, α,β-unsaturated esters, alkenenitriles and imines through a simple and general protocol. The following noteworthy features of this methodology should be emphasized:

a) the reaction is of general applicability to the addition of the P-H bond to unsaturated systems;
b) the catalyst is commercially available and inexpensive;
c) great operational simplicity: short reaction times between 0°C and room temperature, anhydrous solvents or reagents and inert atmosphere conditions are not required.

We are currently investigating the enantioselective version of the TMG-catalyzed addition of dialkyl phosphites to unsaturated chiral substrates having as the main focus the synthesis of optically pure α–aminophosphonic acids .

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