

Strong Bicyclic Guanidine Base-Promoted Wittig and Horner–Wadsworth–Emmons Reactions

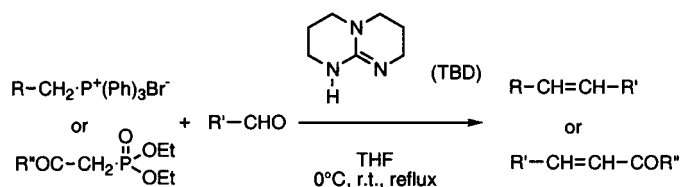
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ABSTRACT



A convenient procedure to effect the Wittig and Horner–Wadsworth–Emmons reactions employs guanidine TBD and MTBD as base-promoters; mild reaction conditions, high efficiency, and facile isolation of the final products make the present methodology, at least in some cases, a practical alternative to known procedures.

We have recently stated that uncharged nitrogen bases have never achieved the same success as the more widely known ionic bases, and we have suggested that, at least in some cases, their potentialities have not received full recognition.¹ Indeed, simplicity of handling and mildness of reaction conditions render nonionic nitrogen bases excellent tools for generating carbanions, which can in turn participate in interesting and useful transformations, thus allowing new improved synthetic methodologies.

Guanidine bases have been known for some time,^{2–4} but there is still little work on their use as general strong bases

in organic synthesis. It is worth noting that recently chiral bicyclic guanidines have received particular attention as promoters of enantioselectivity.^{5–7} Results from our laboratory demonstrated that tetramethylguanidine (TMG)-catalyzed addition of primary nitroalkanes and dialkyl phosphites to a variety of unsaturated systems constitutes a practical means to perform the nitroaldol reaction (Henry reaction) and to achieve phosphonate synthons.^{8,9}

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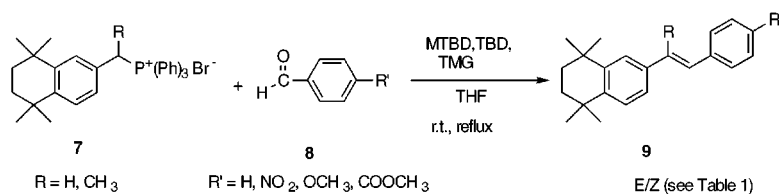
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Scheme 2



Remarkable is that by means of the proposed methodology unstable ylids may be generated in high yields. Indeed, the alkyltriphenylphosphonium salts (entries 1–6) reacted efficiently in the presence of TBD with aromatic aldehydes. On the contrary, reaction with aliphatic aldehydes resulted in low yields, possibly as a result of the preferential self-condensation reaction. In this regard, it is worth noting that the reaction with pivalaldehyde offered good yields (entries 11 and 16) of the corresponding alkene. In contrast, ketones are unaffected under these conditions. Additionally, TBD proved also very satisfactory toward generation of stabilized ylids (entries 18–21), and the reaction works very well with both aromatic and aliphatic aldehydes.

Of interest, with more reactive aldehydes (entries 1, 2, 10, and 15), the reaction was completed in a few hours at 0 °C. We were also very surprised to ascertain that in many cases anhydrous solvents or reagents and inert atmosphere conditions are not required. Since it is well-known that benzylidene-triphenylphosphorane, for example, reacts with water to give triphenylphosphine oxide and toluene, whereas its reaction with oxygen gives the carbonyl compound and triphenylphosphine oxide, it seems reasonable to hypothesize that when more electrophilic aldehydes are used, the reaction with the phosphorane counterpart is faster than that with water and oxygen; on the other hand, the presence of small amounts of water do not affect the reactivity of the base. As a consequence, in the case of reactive aldehydes, only a slightly decrease of the yield was observed when the reaction was carried out in the absence of inert conditions.

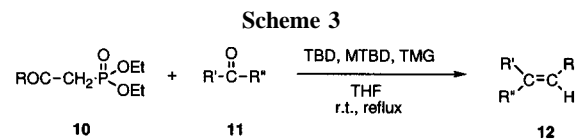
An example is seen in the synthesis of some stilbene derivatives structurally related to the known vitamin A analogue TTNPB **9** (R = Me, R' = CO₂Me). As we recently needed access to a novel class of stilbene analogues of vitamin A, our attention was drawn by the idea that the strong bicyclic guanidine bases TBD or MTBD could be effective promoters of the reaction between the phosphonium salts **7** and the *p*-methoxycarbonylbenzaldehyde **8** (Scheme 2). Thus, while over the years this reaction has been largely described by means of strong ionic bases in an inert atmosphere, we found that with TBD the corresponding stilbene derivatives may be obtained in appreciable yields, comparable with and in many cases superior to those described in the literature. In particular TTNPB was obtained in 55% yield, whereas its demethyl analogue **9** (R = H, R' = CO₂Me) produced 90% yield.¹⁵ Interestingly, compound **9** was also obtained in 83% yield in the absence of anhydrous conditions.

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Concerning the use of MTBD, we found that less reactive aldehydes such as the *p*-methoxybenzaldehyde, as well as benzaldehyde, gave rise to the corresponding olefines in modest yields. With aliphatic aldehydes complex mixtures of products were obtained as a result of the concomitant side aldol reaction.

However, MTBD was demonstrated to be an interesting promoter with more reactive aldehydes; in some cases the reaction produced high yields also at 0 °C, and we did not observe any appreciable difference between MTBD and TBD. Additionally, as phosphonium salts bearing β -electron-withdrawing groups are more readily deprotonated than the corresponding alkyltriphenylphosphonium salts, TBD and MTBD (entries 18–21) proved also advantageous in generating stabilized ylids. On the contrary, TMG leads in general modest yields with both nonstabilized and stabilized ylids, and only in few cases proved positively as the more basic MTBD. Therefore, since the formation of the phosphorane is a reversible process and its concentration at equilibrium clearly depends on the strength of the base used, it is likely that the greater basicity of TBD may explain its greater reactivity. However, the relatively higher steric hindrance offered by MTBD could also be responsible for the lower yields.

Finally, we have also investigated the behavior of the strong guanidine bases TMG, TBD, and MTBD toward the Horner–Wadsworth–Emmons reaction (Scheme 3). It is



well-known that the reaction of phosphonates **10** with a suitable base gives the corresponding carbanions, which react readily with the carbonyl group of aldehydes and ketones **11** to form an alkene and a water-soluble phosphate ester. Since phosphonates are relatively strong acid compounds, it was easy to hypothesize that strong guanidine bases could effectively deprotonate such derivatives. To this regard, it is worth noting that a closer reaction has been reported to occur utilizing LiCl and an amine, e.g., DBU or diisopro-

Table 2. Yields of Horner–Wadsworth–Emmons Reactions, as in Scheme 3

	R	R'	R''	yield ^a		
				MTBD	TBD	TMG
1	CO ₂ Et	H	C ₆ H ₅	87 ^b	92 ^b	75 ^b
2	CO ₂ Et	H	C ₆ H ₁₃	71	80	68
3 ^c	CO ₂ Et	CH ₃	(CH ₂) ₅			
4 ^c	CO ₂ Et	CH ₃	C ₉ H ₁₉			
5	COC ₅ H ₁₁	H	C ₆ H ₅	83	88	71
6	COC ₅ H ₁₁	H	C ₆ H ₁₃	80	79	70
7	CN	H	C ₆ H ₄ 4-NO ₂	ND	100	ND

^a When not specified the reaction occurs in THF at reflux for 24 h. ^b Room temperature for 5 h. ^c No condensation products were detected. All reactions except entry 7 gave only the *E* stereochemistry. Entry 7 gave a mixture 4/6 of the *Z/E* olefine.

pylethylamine (DIPEA), proving of particular interest for use with base-sensitive aldehydes and phosphonates.¹⁶

Briefly, the reaction promoted by TBD and MTBD works very well with both aromatic and aliphatic aldehydes (Table 2); we found the same pattern of reactivity as described above for stabilized ylids, and TMG proved less satisfactory than TBD. However, very surprisingly and clearly in conflict with the known reactivity of phosphonates with ketones, cyclohexanone and aliphatic ketones failed to give the olefination reaction; the yields were unexpectedly low. Finally, as lithium cations affect the course of the Wittig reaction and its modified version, the Horner–Wadsworth–Emmons

(16) Blanchette, M. A.; Choy, W.; Davis, J. T. *Tetrahedron Lett.* **1984**, 251, 2183.

reaction, efforts were also devoted to study possible effects of LiCl in our olefination procedures. Quite surprisingly, under the same conditions as described in the literature,¹⁶ the presence of LiCl did not affect positively the course of our reactions.

In summary, as shown in Tables 1 and 2, the present methodology is particularly suitable using phosphonium salts and phosphonates in the presence of aromatic and, in some cases, aliphatic aldehydes. When phosphonates are utilized results are comparable with those described previously by means of DBU and DIPEA in the presence of LiCl.¹⁶ The steric course of the reaction is in general the same observed with the strong ionic bases. Importantly, the reaction conditions are compatible with many common functional groups. Indeed, substrates containing ether, ester, or nitro groups are suitable substrates and furnish in good yields the desired alkene derivatives. In many cases, anhydrous or inert conditions are not required. There is also the practical advantage that TBD and MTBD are commercially available, and they were used, in all of the described entries, without any additional purification. Therefore, although the literature enumerates hundreds of different ionic base-promoted Wittig procedures, its simplicity, environmental friendliness, and low costs make our procedure, at least in some cases, a practical alternative. The additional advantages of operation and workup simplicity make this methodology a serious candidate for widespread industrial applications such as generating combinatorial stilbene libraries.

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