Pergamon

Tetrahedron Letters 41 (2000) 1607–1610

TETRAHEDRON LETTERS

1,5,7-Triazabicyclo[4.4.0]dec-1-ene (TBD), 7-methyl-TBD (MTBD) and the polymer-supported TBD (P-TBD): three efficient catalysts for the nitroaldol (Henry) reaction and for the addition of dialkyl phosphites to unsaturated systems

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Received 22 October 1999; accepted 16 December 1999

Abstract

The 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and its 7-methyl derivative (MTBD) have been proven to be of great synthetic utility as catalysts in the nitroaldol (Henry) reaction and for the addition of dialkyl phosphites to a variety of carbonyl compounds. The catalysts were in many cases superior to the parent tetramethylguanidine (TMG). In general the reaction proceeds in a few minutes at 0°C. The polymer-supported-TBD (P-TBD) was also proven to be an efficient promoter of the above cited nucleophilic additions. © 2000 Elsevier Science Ltd. All rights reserved.

While a large body of work has been devoted to the study of the chemistry of ionic bases, and their utility in organic synthesis is very well established,[1,2] non-ionic nitrogen bases have never achieved the same success and it is likely that, in many cases, their potential has not received full recognition. However, since they are easy to handle and used under mild reaction conditions, non-ionic nitrogen bases are employed as reagents or catalysts. A great variety of non-ionic bases with weak to medium basic strength and low to very high steric hindrance are available. In many cases these compounds are endowed with very low nucleophilicity so that sterically hindered tertiary amines and amidines are widely used in organic synthesis as proton acceptors.[3,4] Stronger amidine bases DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) also have great synthetic utility and are being extensively used in dehydrohalogenation reactions.[5,6]

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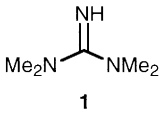
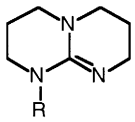
PII: S0040-4039(99)02340-0



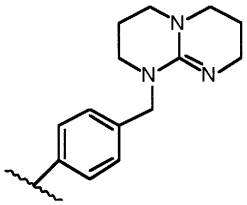
1

TMG



2a,b

a: R = H TBD
b: R = CH_3 MTBD

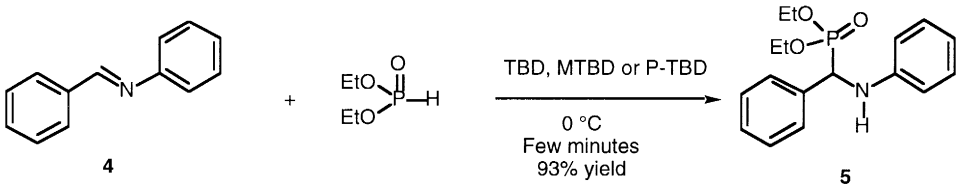


3

Polymer-supported-TBD (P-TBD)

Strong guanidine bases have been known for some time,[7,8] but there is little work on their use as bases in organic synthesis. Results from our laboratory demonstrated that the tetramethylguanidine (TMG)-catalyzed addition of primary nitroalkanes to aldehydes and alicyclic ketones constitutes a practical means to perform the nitroaldol reaction (Henry reaction).[9] Moreover, the TMG-catalyzed addition of dialkyl phosphites to α,β-unsaturated carbonyl compounds, alkenenitriles, aldehydes and ketones was found to provide a practical route to a variety of phosphonate synthons.[10] It is also worth noting that optically pure bicyclic guanidine bases have received particular attention recently as effective promoters in a novel catalytic enantioselective Strecker synthesis of chiral α-amino nitriles and α-amino acids.[11]

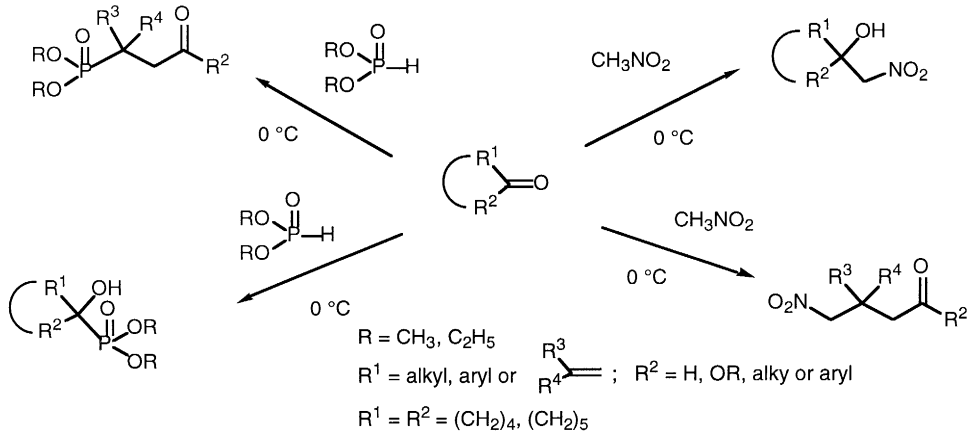
Since the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**2a**) and its methyl derivative MTBD (**2b**) were proven to be ca. 100 times more basic than TMG,[12] and they were widely utilized as powerful organic bases for tautomerizing pyrrocorphins,[13,14] their use as strong, non-ionic, basic catalysts seemed especially interesting for synthetic purposes. In this letter we report our preliminary results concerning the TBD- and MTBD-catalyzed addition of different nucleophiles to a variety of unsaturated systems. Specifically, we explored (Schemes 1 and 2) their utility as strong base catalysts for the addition of dialkyl phosphites (P–H bond) and nitroalkanes to carbonyl compounds such as α,β-unsaturated esters and ketones or saturated aldehydes and ketones as well as to imines. Thus, we have found that the bicyclic guanidine bases TBD and MTBD are superior catalysts for the nitroaldol (Henry) reaction and the addition of dialkyl phosphites to a variety of carbonyl compounds and imines. In addition, the polymer-supported-TBD (P-TBD) was also proven to be an efficient promoter of the above cited additions.



Scheme 1.

We initially choose for our experiments some representative carbonyl compounds which showed greater resistance to undergo the TMG-assisted addition of nucleophiles.[9,10] We focused our attention in particular on alicyclic ketones, imines and some aromatic aldehydes. Afterwards, the reaction was extended to other carbonyl compounds, i.e., α,β-unsaturated ketones and esters as well as to ketones and aldehydes (aromatic and aliphatic). Thus, we were very surprised to ascertain that the addition of diethyl phosphite to benzylideneaniline (**4**) (Scheme 1) occurred in very high yield in just a few minutes at room temperature; moreover, when the reaction was repeated at 0°C the rate and the yield of the reaction were not substantially affected. Likewise, the reaction of cyclohexanone and cyclopentanone with dialkylphosphites (Scheme 2) was equally successful and the corresponding phosphonates were obtained in high yields at 0°C (78% and 75%, respectively).

Additionally, we found that the reaction can be applied successfully to α,β-unsaturated ketones and



Scheme 2.

esters as well as to aromatic and aliphatic ketones or aldehydes (Scheme 2, yields 70–98%);[15] it is worth noting that the reaction also works very well in the presence of the polymer-supported guanidine base P-TBD thus allowing a very simplified work-up of the reaction. As a general rule, the reaction proceeds cleanly under very mild conditions (in general at 0°C) and no side reactions are observed.[16]

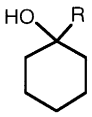
In summary, when compared to the TMG-assisted addition of dialkyl phosphites to carbonyl compounds, the proposed procedure offers significant advantages, especially in terms of milder reaction conditions and shorter reaction times.

Finally, we have also investigated the bicyclic guanidine bases **2a**,**b** as promoters for the nitroaldol (Henry) reaction. In order to avoid problems stemming from the possible production of the unsaturated nitro compounds, as well as to avoid formation of the Nef by-products, the quest for new catalysts to promote the nitroaldol reaction is still the focus of many research interests.[17] In this context, we found that the bicyclic guanidines **2a**,**b** and the polymer-supported P-TBD **3** were very efficient promoters of the addition of nitromethane to aldehydes and alicyclic ketones (Scheme 2). The addition of nitromethane to cyclohexanone was completed in 1 h at 0°C and, usually, the addition produced very high yields also with aldehydes (both aliphatic and aromatic) (80–95%), and with α,β-unsaturated carbonyl compounds (70–90%);[15] the dehydrated by-products were observed only in traces. However, the reaction was not generally applicable as aliphatic ketones and acetophenone did not react in the presence of bicyclic guanidine bases.

In conclusion, we have demonstrated the ability of TBD, MTBD and P-TBD to accomplish the addition of dialkyl phosphites to a variety of carbonyl compounds. We have also demonstrated that these bicyclic guanidine bases are highly efficient promoters of the Henry reaction (Scheme 3: some selected results by means of the TBD base are reported). Thus, we believe that the TBD- and MTBD-catalyzed addition of nucleophiles reported here offers significant advantages over existing methods, especially in terms of milder reaction conditions and shorter reaction times.

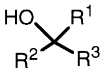
To the best of our knowledge, the proposed methodology represents the most effective approach for the preparation of some nitroalkane derivatives such as **6a**[9,18] and **7a**[10] as well as for the aminophosphonate **5**.[10] The use of the polymer-supported P-MTBD may be of particular interest due to the simplicity of the work-up and, in addition, for the nitroaldol reaction, when acidification of the reaction mixture may lead to the Nef reaction.

Future work in this area will extend the study to optically pure bicyclic guanidine, it is likely that the



6a-c

a: R = CH_2NO_2 (82%, 0 °C, 1h)
b: R = $CH(CH_3)NO_2$ (70%, 0 °C, 5h)
c: R = PO_3Et_2 (78%, 0 °C, 3h)



7a-d

a: $R^1 = CH_2NO_2$, R^2 = Ph, R^3 = H (95%, 0 °C, 5 min.)
b: $R^1 = CH_2NO_2$, $R^2 = nC_4H_9$, R^3 = H (75%, 0 °C, 1h)
c: $R^1 = PO_3Et_2$, R^2 = Ph, R^3 = H (98%, 0 °C, 1h)
d: $R^1 = PO_3Et_2$, $R^2 = nC_5H_{11}$, $R^3 = CH_3$ (95%, 0 °C, 1h)

Scheme 3.

use of such chiral bases may induce, at least in part, enantiospecificity in the above described addition reactions.

Acknowledgements

This work was in part supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Rome)

References

1. House, H. O. *Modern Synthetic Reactions*; Benjamin: Menlo Park, California, 1972; 2nd edn, pp. 492–546.
2. Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, 1986; 3rd edn, pp. 1–26.
3. Eisele, G.; Simchen, G. *Synthesis* **1978**, 757.
4. Sommer, H. Z.; Lipp, H. I.; Jackson, L. L. *J. Org. Chem.* **1971**, *36*, 824.
5. Sternbach, D.; Shibuya, M.; Jaisli, F.; Bonetti, M.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 634.
6. Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, 591.
7. Smith, P. A. S. In *The Chemistry of Open Chain Nitrogen Compounds*; Benjamin: New York, 1965, Vol. 1, Chapter 6, pp. 233–290.
8. Barton, D. H. R.; Elliott, J. D.; Géro, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085.
9. Simoni, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749 and references cited therein.
10. Simoni, D.; Invidiata, F. P.; Manferdini, M.; Lampronti, I.; Rondanin, R.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1998**, *39*, 7615 and references cited therein.
11. Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.
12. Schwesinger, R. *Chimia* **1985**, *39*, 169.
13. Johansen, J. E.; Piermattie, V.; Angst, C.; Diener, E.; Kratky, C; Eschenmoser, A. *Angew. Chem., Int. Ed., Engl.* **1981**, *20*, 261.
14. Angst, C.; Kratky, C.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 263.
15. The catalyzed addition of diethyl phosphite and nitromethane to methyl vinyl ketone, methyl acrylate and methyl crotonate proceeded by means of TBD in 85, 96, 79, 98, 95 and 72% yield, respectively.
16. Experimental procedure. The addition reactions were performed neat at 0°C: the carbonyl compound (10 mmol) and the dialkyl phosphite (or the nitroalkane) (5 ml) were mixed together in the presence of a catalytic amount (10%) of the bicyclic guanidine base, and the reaction was stirred. At the end of the reaction the mixture was diluted with diethyl ether, washed with 5% HCl, dried over sodium sulphate and distilled under vacuum.
17. Kinsaga, P. B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298 and references cited therein.
18. Dauben Jr., H. J.; Ringold, H. J.; Wade, R. H.; Pearson, D. L.; Anderson Jr., A. G. *Org. Synth., Coll. Vol.* **1963**, *4*, 221.