TMEDA Catalyzed Henry (Nitroaldol) Reaction under Metal and Solvent-free Conditions

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Received May 21, 2009, Accepted June 23, 2009

The Henry (nitroaldol) reaction proceeds under mild conditions with catalytic amount of tetramethylethylenediamine (TMEDA) to afford β-nitro alkanol in considerably excellent yield. Structurally diverse aldehydes can be converted into 1,2-amino alcohols, amino sugars, nitroketones, nitroalkenes, ketones (Nef reaction), and other important compounds. Particularly, nitroaldol adducts of enantiopure α-amino aldehydes can be readily converted into pharmacologically important molecules such as the anti-HIV drug amprenavir as well as α-hydroxy-β-amino acids, a valuable backbone of peptide mimetics.

Key Words: TMEDA, Nitroaldol, Solvent-free, β-Nitro alkanol

Introduction

The Henry (nitroaldol) reaction1 is a powerful carbon-carbon bond-forming reaction that can be used to create a new stereogenic center at the β-position of nitro functionality.2 The synthetic utility of the nitro-aldol reaction is based on the versatility of the 1,2-nitro alcohols, which can be converted into 1,2-amino alcohols, amino sugars, nitroketones, nitroalkenes, ketones (Nef reaction), and other important compounds. Particularly, nitroaldol adducts of enantiopure α-amino aldehydes can be readily converted into pharmacologically important molecules such as the anti-HIV drug amprenavir as well as α-hydroxy-β-amino acids, a valuable backbone of peptide mimetics.

There are several reviews concerning the Henry reaction.5 The reaction is generally performed in the presence of bases such as sodium methoxide, sodium hydroxide, sodium carbonate, barium hydroxide, tetrabutylammonium hydroxide, triethylamine, LDA, and butyl lithium. Numerous organocatalysts usually contain trivalent nitrogen6 that have different modes of action such as secondary amine catalysis via enamines and iminium ion.

The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their low cost and low toxicity, which confer a huge benefit for the pharmaceutical intermediates when compared with transition metal.

Although supercritical carbon dioxide, ionic liquid and water have been extensively studied, solvent-free condition is definitely the best option. Development of solvent-free organic reaction is thus gaining prominence.7 Therefore, alternative procedure for the preparation of Henry-type adducts that obviates the use of metallic catalyst and organic solvent would be of great interest.8

N,N,N’,N’-tetramethylethylenediamine (TMEDA) can be classified as an organic base like amines and amidines, and regarded as a strong base9 due to the resonance stability of their conjugate acid.10 Recently Zhang et al. reported that TMEDA promotes the synthesis of thiourea and its derivatives.11 TMEDA was also used as an effective catalyst in combination with CoCl2 for hydrosilylation of acrylonitrile.12 Nishiyama et al. reported that TMEDA acts as a powerful ligand for the hydrosilylation of ketones.13 TMEDA promotes regioselective ring opening of aziridines with silylated nucleophiles. Klein et al. chose TMEDA as promoters for nitroaldol reaction in presence of diethylzinc.14

Results and Discussion

As a part of our on-going interest for development of useful synthetic methodologies15 we wish to herein report a simple method for the synthesis of racemic β-nitro alkanols in the presence of a catalytic amount (0.3 equiv) of TMEDA at rt under solvent-free condition (Scheme 1). The Henry reactions with the aldehyde (1 equiv) and nitromethane (1 equiv) catalyzed by TMEDA (0.3 equiv) are summarized in Table 1. P- and m-Chloro benzaldehyde do not show any electronic and substituent effects on yield (entry 2 and 3). While o-chloro benzaldehyde need quite longer reaction time relative to p- and m-chloro benzaldehyde (entry 4). Unsubstituted aldehydes like benzaldehyde and naphthaldehyde produce the products smoothly with excellent yield. Naphthaldehyde however, needs “longer” reaction time relative to benzaldehyde (entry 1 and 9). Cyano-and nitrobenzaldehyde are able to produce nitroaldol product with considerably high yield in “relatively” short reaction time (entry 5 and 6). A large scale (10.0 g) synthesis of nitro aldol product is also carried out and the reaction proceeds in relatively longer reaction time with high yield (entry 1 and 6). Cinnamaldehyde is also able to give nitroalldol product with quite high yield (entry 10). Butyraldehyde and cyclohexane carboxaldehyde need quite longer reaction time with lower yield relative to aromatic aldheyde (entry 11 and 12). In addition to the aromatic and aliphatic aldehyde, heteroaromatic furfuraldehyde also results in good yield of nitro aldo product with longer reaction time (entry 14).

The generality and the excellence of TMEDA can be easily

Scheme 1. Henry reaction catalyzed by TMEDA
Table 1. Henery reaction between aldehydes and nitromethane with TMEDA as the catalyst.\textsuperscript{a}

<table>
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<th>Entry</th>
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\textsuperscript{a}Reaction condition: Aldehyde (1.0 equiv), Nitromethane (1.0 equiv), TMEDA (0.3 equiv). \textsuperscript{b}Isolated yield. \textsuperscript{c}Large scale reaction employs 10.0 mmol of aldehyde.
reflected from the comparison with literature results. Phosphine needs 10 mol% for the production of 56 - 84% nitroalcohol product in methanol as solvent. Mg: Al demands 5 h reaction time at 60 °C for the 74 - 94% yield. TTMPP [tris(2,4,6-trimethoxyphenyl)phosphine] requires 20 mol% as a catalyst for nitroalcohol product at 20 - 30 °C within 8 - 100 h reaction time for 70 - 96% yield. Guanidine claims 10 mol % of catalyst for 74 - 98% yield within 5 min to 24 h reaction time. These results clearly indicate that present catalytic method is superior in terms of reaction time, yield and solvent-free condition at rt.

Conclusions

In conclusion, we have described TMEDA as a useful and highly effective catalyst for Henry reaction under metal and solvent-free condition at rt. Aromatic, aliphatic and heterocyclic aldehydes are able to produce nitroalcohol product with excellent yield in short reaction time. This also avoids the use of hazardous acid, metal catalyst and expensive Lewis acids.

Experimental

General. In all cases the 1H NMR (200 MHz) spectra were recorded with Varian Gemini 200 instrument. Chemical shifts are reported in ppm with TMS as an internal standard. 13C NMR data were collected on a Varian Gemini 400 instrument. Chemical shifts are reported in ppm in CDCl3 with TMS as an internal standard.


5.51-5.49 (m, 1H), 4.59-4.48 (m, 2H), 2.49 (bs, 1H). 13C NMR (CDCl3, 50 MHz): 157.86, 140.45, 130.29, 129.83, 123.71, 12.36, 119.11, 118.73, 115.97, 70.50. MS (EI') m/z (%): 259, 212, 198.

1H NMR (CDCl3, 200 MHz): 7.38-7.23 (m, 2H), 6.91-6.99 (m, 2H), 5.58 (m, 1H), 4.78 (dd, J = 13.5Hz, 3.2 Hz, 1H), 4.57 (dd, J = 13.3 Hz, 8.0 Hz, 1H), 4.95 (bs, 1H), 3.92 (s, 3H). 13C NMR (CDCl3, 50 MHz): 138.24, 132.56, 128.76, 129.78, 126.13, 124.04, 70.20. MS (EI) m/z (%): 145, 130, 102, 76, 50.
1-(Furan-2-yl)-2-nitroethanol (entry 14) 18. 1H NMR (CDCl3, 200 MHz): 7.41-7.38 (m, 1H), 6.40-6.37 (m, 1H), 6.33-6.27 (m, 1H), 5.48-5.44 (m, 2H), 4.73-4.64L (m, 1H), 4.42 (bs, 1H), 3.20 (s, 3H). 13C NMR (CDCl3, 50 MHz): 150.74, 143.41, 129.37, 110.80, 1770 (m, 1H), 5.48-5.44 (m, 2H), 4.73-4.64 (m, 1H), 4.42 (bs, 1H).

**Acknowledgments.** Authors thank the Centre for Biological Modulators from KRICT for the financial assistance. This work also has been supported by BK 21 of Korea Research Council.

**References**