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

Anjoy Majhi, Santosh T. Kadam, and Sung Soo Kim*

*Department of Chemistry, Inha University, Incheon 402-751, Korea. *E-mail: sungsoo@inha.ac.kr*
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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 react with nitromethane in presence of 0.3 equiv of TMEDA under solvent-free condition at rt. The low catalytic loading and mild reaction condition are the key features of the catalytic method.

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

Introduction

The Henry (nitroaldol) reaction[1] 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.[3] 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.[4]

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, tetrabutylamonium hydroxide, triethylamine, LDA, and butyl lithium. Numerous organocatalysts usually contain trivalent nitrogen[6] 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.

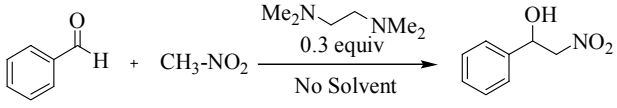
Although supercritical carbon dioxide, ionic liquid and water have been extensively studied, solvent-free condition is definitely the best option. Development of solvent-free organic reaction is thus gaining prominence.[7] Therefore, alternative procedure for the preparation of Henry-type adducts that 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 base[9] 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 $CoCl_2$ 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

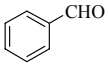
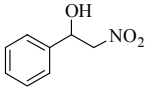
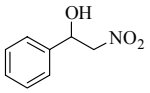
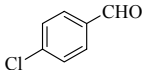
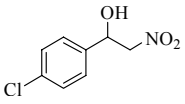
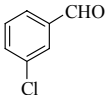
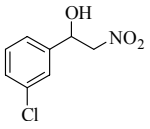
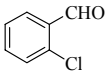
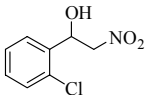
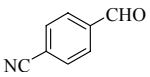
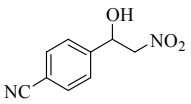
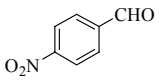
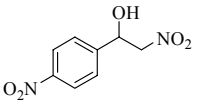
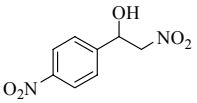
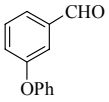
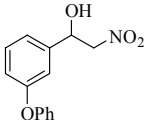
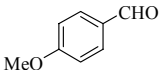
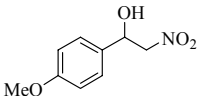
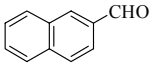
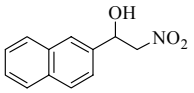
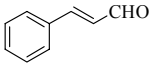
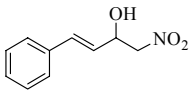
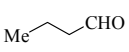
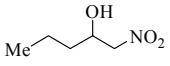
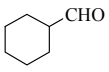
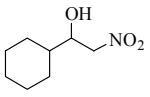
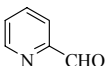
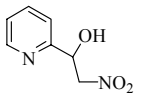
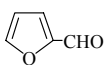
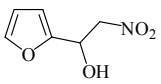
As a part of our on-going interest for development of useful synthetic methodologies[15] we wish to herein report a simple method for the synthesis of racemic β-nitro alkanols in the presence of a catalytic amount (0.3 equiv) of TMEDA at rt under solvent-free condition (Scheme 1). The Henry reactions 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 nitroaldol product with quite high yield (entry 10). Butylaldehyde and cyclohexane carboxaldehyde need quite longer reaction time with lower yield relative to aromatic aldehyde (entry 11 and 12). In addition to the aromatic and aliphatic aldehyde, heteroaromatic furfuraldehyde also results in good yield of nitro aldol 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.[a]

Entry	Substrate	Product	Time (min)	Yield (%)[b]
1			30	92
			2 h[c]	87[c]
2			55	77
3			50	92
4			95	72
5			15	90
6			12	98
			50[c]	91[c]
7			2 h	80
8			2 h	93
9			80	96
10			40	98
11			6 h	54
12			4 h	42
13			30	97
14			70	79

[a]Reaction condition: Aldehyde (1.0 equiv), Nitromethane (1.0 equiv), TMEDA (0.3 equiv). [b]Isolated yield. [c]Large scale reaction employs 10.0 mmol of aldehyde.

reflected from the comparison with literature results.[15-18] Phosphine needs 10 mol% for the production of 56 - 84% nitroaldol product in methanol as solvent.[16] 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 nitroaldol product at 20 - 30 °C within 8 - 100 h reaction time for 70 - 96% yield.[18] Guanidine claims 10 mol % of catalyst for 74 - 98% yield within 5 min to 24 h reaction time.[19] These results clearly indicate that present catalytic method is superior in terms of reaction time, yield and metal 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 nitroaldol 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 ^{1}H NMR (200 MHz) spectra were recorded with Varian Gemini 200 instrument. Chemical shifts are reported in ppm in $CDCl_3$ with TMS as an internal standard. ^{13}C NMR data were collected on a Varian Gemini 400 instrument (400 MHz). Some compounds are also identified by HRMS (EI) with Jeol DMX 303 and GCMS (EI 70 eV). Low resolution mass spectra by use of EI^+ (Electronic Impact Ionization) were obtained on 1200L Single Quadrupole GC/MS System with 3800GC/Varian.

Reaction Procedure for Henery reaction. To a mixture of aldehyde (1 equiv) and nitromethane (1 equiv) was added TMEDA (0.3 equiv). The reaction mixture was stirred at rt for the appropriate time (Table 1). The completion of the reaction was monitored with TLC. Water was added after completion of reaction that was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated to be purified by column chromatography with silica gel.

The spectral (^{1}H, ^{13}C NMR, LRMS and HRMS) data of products are given below. All products are reported in literature.[17,18,19,20]

2-Nitro-1-phenylethanol (entry 1)[18]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.41-7.34 (m, 5H), 5.45 (dd, J = 6, 3.3 Hz, 1H), 4.49-4.43 (m, 2H), 4.22 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) 138.4, 129.2, 128.6, 126.0, 79.12. MS (EI^+) *m/z* (%): 167, 149, 134, 120, 77, 51.

1-(4-Chlorophenyl)-2-nitroethanol (entry 2)[17]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.38-7.32 (m, 4H), 5.45-5.42 (m, 1H), 4.59-4.46 (m, 2H), 4.38 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 140.12, 134.86, 130.24, 129.78, 126.13, 70.20. MS (EI^+) *m/z* (%): 201, 184, 154, 141, 91, 77.

1-(3-Chlorophenyl)-2-nitroethanol (entry 3)[17]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.50-7.48 (m, 4H), 5.51-5.49 (m, 1H), 4.46-4.41 (m, 2H), 4.28 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 140.12, 134.86, 130.24, 129.78, 129.32, 126.13, 124.04, 70.20.

1-(2-Chlorophenyl)-2-nitroethanol (entry 4)[17]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.50-7.48 (m, 4H), 5.51-5.49 (m, 1H), 4.46-4.41 (m, 2H), 4.41 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 138.24, 132.56, 128.76, 129.14, 129.78, 126.13, 124.04, 70.31.

4-(1-Hydroxy-2-nitroethyl) benzonitrile (entry 5)[18]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.71-7.68 (m, 2H), 7.56-7.54 (m, 2H), 5.55-5.52 (m, 1H), 4.57-4.51 (m, 2H), 3.29 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 143.26, 132.89, 132.74, 126.71, 118.19, 112.66, 70.07. MS (EI^+) *m/z* (%): 145, 130, 102, 76, 50.

2-Nitro-1-(4-nitrophenyl) ethanol (entry 6)[18]: ^{1}H NMR ($CDCl_3$, 200 MHz): 8.18 (d, J = 8 Hz, 2H), 7.59 (m, 2H), 5.58-5.61 (m, 1H), 4.57-4.59 (m, 2H), 3.12 (bs, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz): 147.83, 145.31, 126.91, 123.99, 80.59, 69.88. HRMS found: *m/z* [M+H] 212.0418 $C_8H_8N_2O_5$ requires: 212.0433. MS (EI^+) *m/z* (%): 165, 151, 135, 120, 105, 91.

2-Nitro-1-(3-phenoxyphenyl) ethanol (entry 7)[20]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.37-6.96 (m, 9H), 5.43-5.40 (m, 1H), 4.59-4.48 (m, 2H), 2.49 (bs, 1H). ^{13}C NMR ($CDCl_3$, 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.

1-(4-Methoxyphenyl)-2-nitroethanol (entry 8)[17]: ^{1}H NMR ($CDCl_3$, 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). ^{13}C NMR ($CDCl_3$, 50 MHz): 159.96, 130.214, 128.478, 127.243, 114.333, 70.617, 55.297. MS (EI^+) *m/z* (%): 197, 193, 150, 137, 110. HRMS found: *m/z* [M+H] 197.0690. $C_9H_{11}NO_4$ requires: 197.0688).

1-(2-Naphthyl)-2-nitroethanol (entry 9)[18]: ^{1}H NMR ($CDCl_3$, 200 MHz): 8.00-7.94 (m, 1H), 7.91-7.88 (m, 1H), 7.85-7.84 (m, 1H), 7.73-7.71 (m, 1H), 7.26-7.30 (m, 3H), 6.27-6.24 (m, 1H), 4.68-4.65 (m, 2H), 2.89 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 133.69, 133.52, 129.51, 129.35, 129.03, 126.02, 124.46, 123.82, 121.79, 80.76, 68.26. MS (EI^+) *m/z* (%): 217, 170, 157, 153. HRMS found: *m/z* [M+H] 217.0738 $C_{12}H_{11}NO_3$ requires 217.0739.

(E)-1-Nitro-4-phenylbut-3-en-2-ol (entry 10)[17]: ^{1}H NMR ($CDCl_3$, 200 MHz): 7.40-7.31 (m, 5H), 6.17 (d, J = 16.9 Hz, 1H), 6.11 (d, J = 15.5 Hz, 1H), 5.08-5.01 (m, 1H), 4.58 (d, J = 6 Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz): 135.48, 133.61, 128.70, 128.48, 126.68, 124.93, 79.85, 69.55. MS (EI^+) *m/z* (%): 193, 175, 131, 105, 91, 77.

1-Nitropentane-2-ol (entry 11)[19]: ^{1}H NMR ($CDCl_3$, 200 MHz): 4.42 (dd, J = 13.1, 2.9 Hz, 1H), 4.36 (dd, J = 13.1, 8.3 Hz, 1H), 4.32-4.28 (m, 1H), 2.94 (bs, 1H), 1.58-1.35 (m, 4H), 0.90 (t, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): 80.67, 68.38, 35.04, 19.40, 13.93. MS (EI^+) *m/z* (%): 90, 73, 69, 62.

1-Cyclohexyl-2-nitroethanol (entry 12)[17]: ^{1}H NMR ($CDCl_3$, 200 MHz): 4.52-4.39 (m, 2H), 4.10-4.04 (m, 1H), 2.89 (bs, 1H), 1.80-1.63 (m, 5H), 1.50-1.39 (m, 1H), 1.25-1.01 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): 79.5, 73.0, 41.6, 28.9, 28.1, 26.3, 26.0, 25.7. MS (EI^+) *m/z* (%): 127, 75, 67,45.

2-Nitro-1-(pyridine-2-yl) ethanol (entry 13)[17]: ^{1}H NMR ($CDCl_3$, 200 MHz): 8.54-8.52 (m, 1H), 7.77-7.72 (m, 1H), 7.47-7.45 (m, 1H), 7.29-7.25 (m, 1H), 5.48-5.44 (m, 1H), 4.80-4.75 (dd, J = 13.2, 9.6 Hz, 1H), 4.65-4.89 (dd, J = 13.2, 9.6 Hz, 1H), 4.23 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 156.71, 148.77, 137.53, 123.55, 120.94, 70.36. HRMS calcd for $C_7H_8N_2O_3$: 168.0535 Found: 168.0541.

1-(Furan-2-yl)-2-nitroethanol (entry 14)[18]: ^{1}H NMR ($CDCl_3$, 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), 4.73-4.64 (m, 1H), 4.42 (bs, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 150.74, 143.41, 129.37, 110.80, 108.82, 74.57. MS (EI^+) *m/z* (%): 153, 110, 97, 83, 81.

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