

Henry Reaction in Aqueous Media: Chemoselective Addition of Aldehydes

Cun Liu ZHOU, Yu Qing ZHOU, Zhi Yong WANG*

Department of Chemistry, University of Science & Technology of China, Hefei 230026

Abstract: The chemoselective addition of aldehydes in aqueous medium was obtained under mild condition using improved Henry reaction.

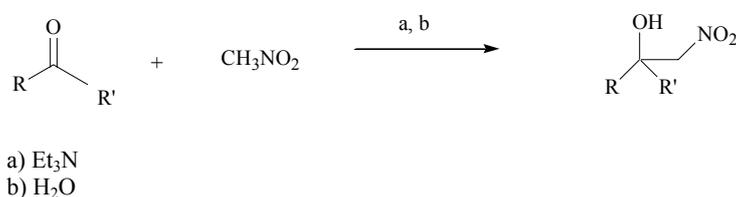
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The Henry or nitroaldol reaction is commonly recognized as one of the classical reaction in organic synthesis¹. The nitroaldol reaction thus developed has found increasing applications in pharmaceutical industries², synthesis of natural products³, polyamino-alcohols and polyhydroxylated amides⁴. The pursuit of all these synthetic targets with increasing complexity has resulted in the development of reactions that emphasize chemo-, regio-, diastereo-, and enantioselectivity. In defining the strategies and reactions to construct complex molecules, chemoselectivity is required⁵. However, the classical nitroaldol reaction performed in organic solvent in the presence of base has low chemoselectivity among different carbonyl compounds⁶. The basic reagents often make the nitroaldol reaction to side reactions such as aldol condensation, Cannizzaro reaction. Also, the volatile and toxic organic solvents have an impact on the environment. Thus it is necessary to adopt environmental friendly conditions to impress these competitive reactions without compromising the yield. Previously, Ballini and co-workers reported the use of cetyltrimethylammonium chloride as a phase-transfer agent for nitroaldol reactions in water containing sodium hydroxide⁷. Varma *et al.* carried out Henry reaction under microwave condition in absence of any solvent⁸. To the best of our knowledge, there is no any report about the chemoselectivity of nitroaldol reaction in water. Recently our efforts have shown that it is possible for nitroaldol reaction in water with certain chemoselectivity. Here, we report an unprecedented chemoselectivity of nitroaldol reaction between aldehyde and ketone in mild base-promoted condition.

In our work, we have chosen triethylamine as a base. Standard procedure for Henry reaction was showed as following. Benzaldehyde (1.0 mmol) was stirred with nitromethane (1.5 mmol) and triethylamine (1.0 mmol) in 5.0 mL water for 6.0 h at room temperature. The reaction was stopped and followed by extracting with diethyl ether 3

*E-mail: zwang3@ustc.edu.cn

mL (x3). After being dried over magnesium sulfate, the solution was filtered and concentrated under vacuum to give the crude product, which was subsequently purified by flash chromatography on silica gel to give 81% of the corresponding product. Subsequently, a variety of carbonyl compounds were tested with this method (**Scheme 1**). The results are listed in **Table 1**.

Scheme 1**Table 1** Henry reaction in aqueous media⁹

Entry	R	R'	Yield(%)	Time(h)
1	ph-	H-	81	6.0
2	2-naphth-	H-	88	5.0
3	Pipero-	H-	75	3.0
4	4-Me-ph-	H-	72	8.0
5	4-MeO-ph-	H-	26	8.5
6	4-Cl-ph-	H-	71	3.0
7	Furan-	H-	45	6.5
8	CH ₃ (CH ₂) ₅ -	H-	79	7.0
9	4-NO ₂ -ph-	H-	86	3.0
10	4-Me ₂ N-ph-	H-	0	12
11	Ph-	CH ₃ -	0	12
12	CH ₃ CH ₂ -	CH ₃ -	0	12

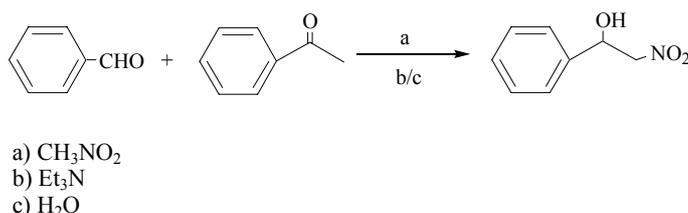
a: Isolated yield

It was found that both aromatic and aliphatic aldehydes reacted efficiently with nitromethane promoted by triethylamine in water. It is noteworthy to mention that aromatic aldehydes bearing halogens, methoxyl, nitro or other group reacted without any problem (Entry 3-6, 9). Electron withdrawing groups (such as -Cl, -NO₂) at *para*-position favor the reaction whereas the electron donating groups (such as Me₂N-) are unfavorable to the reaction. On the other hand, aryl and aliphatic ketone appeared to be inert under the same reaction conditions (Entry 11, 12). Such an unusual difference of reactivity between an aldehyde and a ketone indicated that Henry reaction in this condition possesses unprecedented chemoselectivity.

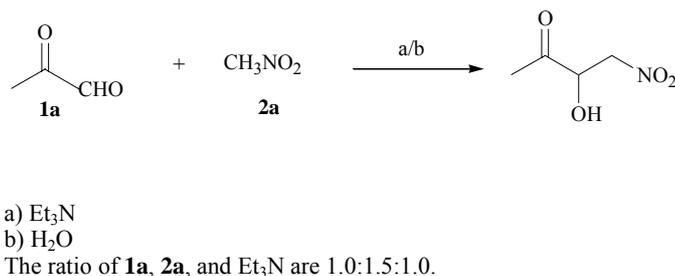
For proving this hypothesis, we carried out this reaction with mixture of benzaldehyde (1.0 mmol), acetophenone (1.0 mmol) and nitromethane (3.0 mmol) under the same condition (**Scheme 2**). Only benzaldehyde reacted smoothly with nitromethane. An intramolecular discrimination study has also been carried out on a compound bearing both aldehyde and ketone group under standard condition, a complete chemoselectivity

was observed (**Scheme 3**). The reaction occurred exclusively on the aldehyde group and gave the corresponding aldol addition product in 76% yield¹⁰.

Scheme 2



Scheme 3



In conclusion, we have developed a simple and environmental friendly procedure for the synthesis of various types of β -nitroalcohol compounds. This method offers a complete chemoselectivity toward aldehydes in the presence of ketone.

References and Notes

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- Spectral data of nitroalcohol compounds in **Table 1** is as below.
Entry 1: IR (film cm⁻¹): 3429, 1553. ¹H NMR (CDCl₃, δ ppm): 2.68-2.95 (br, 1H), 4.35-4.60 (m, 2H), 5.29-5.40 (m, 1H), 7.19-7.48 (m, 5H). ¹³C NMR: 78.71, 73.03, 113.68, 117.73, 127.12, 135.09. MS: *m/z* 149 (M-H₂O).
Entry 2: IR (film cm⁻¹): 3416, 1552, 1515. ¹H NMR (CDCl₃, δ ppm): 2.94-3.23 (br, 1H), 4.56-4.60 (m, 1H), 4.46-4.71(m, 1H), 5.59-5.62 (m, 1H), 7.45-7.47 (m, 1H), 7.54-7.56 (m, 2H),

- 7.85-7.89 (m, 4H). ^{13}C NMR: 71.29, 81.36, 123.41, 125.48, 126.84, 126.87, 127.95, 128.25, 129.12, 133.33, 133.54, 135.68. MS: m/z 199 (M-H₂O).
- Entry 3: IR (film cm^{-1}): 3416, 1566, 1541, 1504. ^1H NMR (CDCl_3 , δ ppm): 2.30-2.87 (br, 1H), 4.46-4.50 (m, 1H), 4.56-4.62 (m, 1H), 5.36-5.40 (m, 1H), 6.00 (s, 2H), 6.84 (s, 1H), 6.86-6.87 (m, 1H), 6.90-6.91 (m, 1H). ^{13}C NMR: 70.81, 81.23, 101.39, 106.36, 108.62, 109.14, 119.60, 132.00, 148.25. MS: m/z 193 (M-H₂O).
- Entry 4: IR (film cm^{-1}): 3441, 1553. ^1H NMR (CDCl_3 , δ ppm): 2.37 (s, 3H), 2.63-2.92 (br, 1H), 4.52-4.47 (m, 1H), 4.57-4.61 (m, 1H), 5.40-5.45 (m, 1H), 7.22 (d, 2H, $J=8.00$ Hz), 7.29 (d, 2H, $J=8.00$ Hz). ^{13}C NMR: 70.91, 77.34, 81.25, 125.88, 129.70, 135.17, 138.94. MS: m/z 163 (M-H₂O).
- Entry 5: IR (film cm^{-1}): 3441, 1553. ^1H NMR (CDCl_3 , δ ppm): 2.67-2.94 (br, 1H), 3.79 (s, 3H), 4.46-4.50 (m, 1H), 4.58-4.63 (m, 1H), 5.40-5.43 (m, 1H), 7.14 (d, 2H, $J=8.40$ Hz), 7.33 (d, 2H, $J=8.40$ Hz). ^{13}C NMR: 56.06, 73.12, 84.85, 114.36, 129.32, 135.23, 158.07. MS: m/z 179 (M-H₂O).
- Entry 6: IR (film cm^{-1}): 3431, 1597, 1556. ^1H NMR: 3.17-3.22 (br, 1H), 4.44-4.49 (m, 1H), 4.51-4.58 (m, 1H), 5.37-5.42 (m, 1H), 7.31 (d, 2H, $J=8.40$ Hz), 7.35 (d, 2H, $J=8.40$ Hz). ^{13}C NMR: 70.31, 81.00, 127.35, 129.23, 134.83, 136.60. MS: m/z 184 (M-H₂O).
- Entry 7: IR (film cm^{-1}): 3460, 1556, 1503. ^1H NMR (CDCl_3 , δ ppm): 2.58-2.81 (br, 1H), 4.65-4.70 (m, 1H), 4.75-4.82 (m, 1H), 5.46-5.50 (m, 1H), 6.39-6.61 (m, 2H), 7.43-7.46 (m, 1H). ^{13}C NMR: 64.85, 78.40, 108.22, 110.68, 143.20, 150.70. MS: m/z 139 (M-H₂O).
- Entry 8: IR (film cm^{-1}): 3410, 1555. ^1H NMR (CDCl_3 , δ ppm): 0.85 (t, 3H, $J=7.20$ Hz), 1.18-1.39 (m, 6H), 1.40-1.61 (m, 4H), 2.40-2.96 (br, 1H), 4.22-4.30 (m, 1H), 4.32-4.40 (m, 2H). ^{13}C NMR: 13.95, 22.49, 24.98, 28.95, 31.59, 33.78, 68.79, 80.77. MS: m/z 157 (M-H₂O).
- Entry 9: IR (film cm^{-1}): 3529, 1556, 1519. ^1H NMR (CDCl_3 , δ ppm): 2.99-3.63 (br, 1H), 4.49-4.67 (m, 2H), 5.49-5.81 (m, 1H), 7.63 (d, 2H, $J=8.40$ Hz), 7.27 (d, 2H, $J=8.40$ Hz). ^{13}C NMR: 69.97, 80.67, 124.18, 126.96, 145.07, 148.12. MS: m/z 194 (M-H₂O).
10. The spectral data of the product in **scheme 3** is as follows.
IR (film cm^{-1}): 3457, 1716, 1557. ^1H NMR (CDCl_3 , δ ppm): 2.38 (s, 3H), 4.02-4.19 (br, 1H), 4.57-4.61 (m, 2H), 4.90-4.93 (m, 1H). ^{13}C NMR: 22.78, 76.74, 80.93, 208.13. MS: m/z 115 (M-H₂O).

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