Reductive Intramolecular Henry Reactions Induced by Stryker's Reagent

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Abstract: Conjugate reductions of nitroalkenes by Stryker's reagent are ensued by intramolecular aldol reactions to produce β-nitroalcohols in good yield, constituting the first examples of reductive Henry reactions.

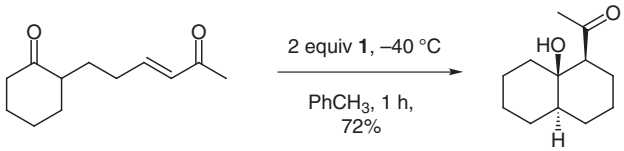
Key words: nitro-aldol reactions, reductions, tandem reactions, copper, nitroalkenes

The Henry reaction is the well known aldol condensation of nitroalkanes with carbonyl compounds and is a classical carbon-carbon bond-forming reaction.[1–4] The β-nitroalcohols thus produced can undergo a range of chemical transformations for the synthesis of β-aminoalcohols, α-hydroxyketones, nitroalkenes and other synthetic intermediates.[5–7] Various reagents have been found to promote these condensations, including quaternary ammonium salts, organic and inorganic bases. While existing nitroaldol and other methodologies readily provide nitroalkenes as electrophilic substrates for further reactions, e. g. Michael additions, their use as nucleophilic reagents is often preceded by conversion to nitroalkanes, an important transformation for which a number of reductive reaction conditions have been developed.[8–11] Recently, an asymmetric reduction of nitroalkenes has also been realized.[12]

We have been engaged in studies to induce a conjugate reduction of nitroalkenes in tandem with a nitroaldol reaction in one operation. These studies were undertaken in the context of recent developments in the conjugate reduction of enones to generate enolates for tandem aldol reactions.[13,14] However, no examples of the analogous Henry reaction using nitroalkenes has appeared in the literature. This reaction may be complicated by concomitant reactions of the nitro group and the electrophile with reducing agents and bases.[12,15] Herein we report the results of our studies.

Nitroalkenone substrates **2a**–**e** were prepared by base-induced Henry reactions of aldehydes with simple nitroalkanes and subsequent dehydration. Although ketones are generally poor electrophiles for the Henry reaction, it has been shown that the intramolecular reaction proceeds satisfactorily.[16] Our approach to the reductive Henry reaction is to engage the nitronate obtained upon conjugate reduction of a nitroalkene by Stryker's reagent $[Ph_3PCuH]_6$ (**1**), to react with a tethered ketone to afford a cyclized aldol product.[17,18] In the event, the reaction of nitroalkene **2a** with 1.5 hydride equivalents of **1** at room temperature was complete in minutes to give a 78% yield of reductively cyclized products. Further investigation of the reaction conditions revealed that the reductive aldol cyclization of **2a** was extremely facile and could be accomplished within one hour at –40 °C.[19] Two fused-ring isomers were formed in a ratio of 5:1. The major isomer was the *cis*-decalin product ***c*-3a**, obtained as a mixture of epimers at the nitro group. The minor product was the *trans*-fused decalin ***t*-3a**. Reductive Henry aldol reactions of various substrates under these reaction conditions are summarized in Table 1. In all of these cases, tandem conjugate reduction proceeded smoothly followed by an intramolecular Henry reaction to give nitroalcohol products with good yields. These are the first examples of reductive Henry reactions. Intramolecular cyclizations to form both six-membered (Table 1, entries 1–3) and five-membered rings (Table 1, entries 4 and 5) were successful.

Compared with the reductive aldol cyclizations of enone substrates induced by **1** (Equation 1),[13a] the diastereoselectivities of the analogous reductive nitroaldol reactions are not as high. Although the reductive reactions were quenched at –40 °C with aqueous NH_4Cl or with precooled 1:1 HOAc–THF, mixtures of diastereomers as well as epimers at the stereocenter α to the nitro group were obtained. The copper counterion provided by **1** did not provide any additional selectivity over the traditional base-induced Henry aldol reactions, which are also not as selective as their enolate aldol corollaries.



Equation 1[13a]

The lack of selectivity is generally attributed to the reversibility of the nitroaldol reaction and the acidity of the α-proton.[6,20] That this reaction is reversible is evidenced by the fact that the diastereomeric ratio of products ***t*-3b** and ***c*-3b** from the reductive cyclization of **2b** was found to deteriorate from 7:1 (Table 1, entry 2) to 4:1 when the reaction time was extended to 24 hours at –40 °C. Any epimerizations of the α-protons at these low temperatures would be attributed to the intermediate aldol alkoxides,

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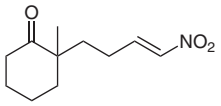
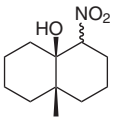
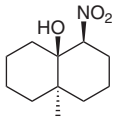
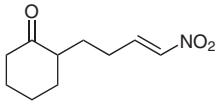
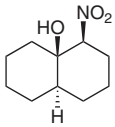
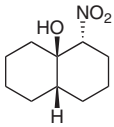
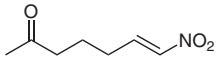
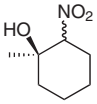
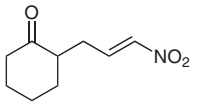
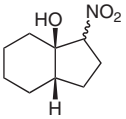
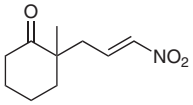
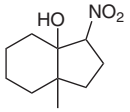
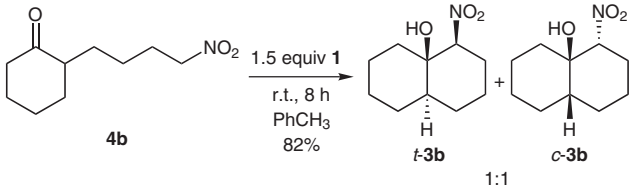
Table 1 Reductive Nitroaldol Cyclizations Induced by **1**

Entry	Substrate	Product (yield,[a] ratio β-NO_2:α-NO_2)	
1	 **2a**		
		***c*-3a** (66%, 1:1)	***t*-3a** (13%)
2	 **2b**		
		***t*-3b** (54%)	***c*-3b** (8%)
3	 **2c**		
		3c (77%, 2:1)	
4	 **2d**		
		3d (74%, 1:2)	
5	 **2e**		
		3e (75%, 3:1)[b]	

[a] Isolated product yields.
[b] Inseparable diastereomeric mixture, stereochemistry not determined.

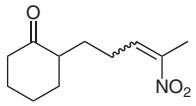
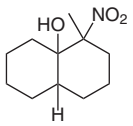
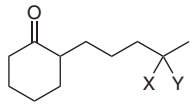
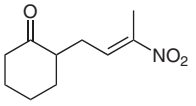
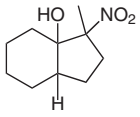
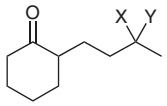
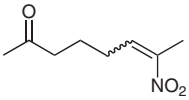
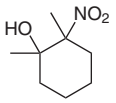
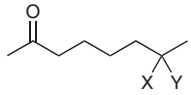
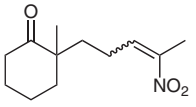
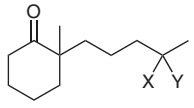
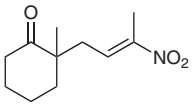
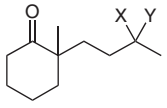
since Stryker's reagent **1** is typically regarded to be a relatively non-basic reagent. However, we have found that at higher temperatures, e. g. room temperature, and over a long reaction time, **1** was able to induce the Henry aldol reaction of nitroalkane substrate **4b** to give the same products as in the reductive cyclization of **2b** in a different ratio (Equation 2).[21]



Equation 2

Nitroalkene substrates having additional substitution at the nitro group were also prepared and subjected to reduction to explore the scope of the reaction (Table 2). The products resulting from these substrates could not be epimerized at the α-stereocenter by deprotonation, although the retro-aldol reaction is still possible. Such substrates were found to undergo both conjugate reduction

Table 2 Reductive Nitroaldol Cyclizations Induced by **1**

Entry	Substrate	Product (yield,[a] ratio of epimers)
1	 **2f** ratio = 2.5:1	 **3f** (75%, 5:1)[b]
		 **4f** X, Y = H, NO_2 (7%)
2	 **2g**	 **3g** (52%, 2:1)[c]
		 **4g** X, Y = H, NO_2 (23%) **5g** X, Y = O (8%)
3	 **2h** ratio = 2:1	 **3h** (25%, 1:1)
		 **4h** X, Y = H, NO_2 (22%) **5h** X, Y = O (27%)
4	 **2i** ratio = 1.2:1	 **4i** X, Y = H, NO_2 (47%) **5i** X, Y = O (33%)
5	 **2j**	 **4j** X, Y = H, NO_2 (39%) **5j** X, Y = O (33%)

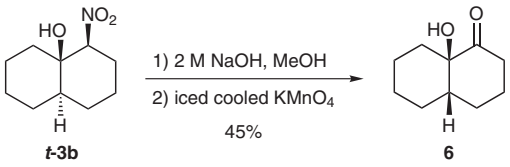
[a] Isolated product yields.
[b] Relative stereochemistry not determined.
[c] Inseparable diastereomeric mixture, stereochemistry not determined.

and cyclization much more sluggishly than those in Table 1. Treatment of **2f** with **1** at –40 °C for 3 hours returned only unreacted starting materials. When the reac-

tion temperature was raised to ambient temperatures, reductive Henry cyclization occurred to give a 75% yield of **3f** as a 5:1 mixture of diastereomers. It was found that additional substituents on the nitroalkene still provided acceptable to good yields of cyclized aldol products (Table 2, entries 1 and 2), and hindered ketones also underwent intramolecular reductive cyclization with unencumbered nitroalkenes (Table 1, entries 2, 4). However, when both of the reaction sites were highly substituted, reduction was possible but cyclization failed to occur (Table 2, entries 4 and 5). With increasing steric hindrance surrounding the reaction sites, simple reduction nitroalkane products **4f–j** were isolated and became the predominant products (Table 2, entries 4 and 5). Also isolated were diketones **5g–j**, which were likely to be derived from Nef reactions of the copper nitronate intermediates of **4f–j** during workup.

The reductive nitroaldol intermediate before quenching is a putative copper nitronate. If copper were able to stabilize the nitronate, a subsequent Nef reaction may be favored, leading to a one-pot reductive Henry–Nef reaction.[22] However, subjecting the reduction mixture to the Nef conditions was found to be plagued by many side reactions, including the retro-aldol reaction. After workup, nitroalcohols such as ***t*-3b** could be transformed in a separate reaction into α-hydroxyketone **6**[23] via a Nef reaction with a concomitant retro-aldol reaction (Equation 3).

In summary, we have accomplished the first reductive Henry aldol reactions using Stryker's reagent **1**.



***t*-3b** **6**

Equation 3

Acknowledgment

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(19) **Typical Experiment Procedure:** Compound **1** (1.5 hydride equiv) was transferred to a dry flask inside a dry box. Toluene (2 mL) was added and the resulting red solution was cooled to –40 °C. Nitroalkene **2a** (0.6 mmol) in 2 mL toluene was added to **1** via cannula. After 1 h, the reaction was quenched by adding 2 mL sat. aq NH_4Cl and stirred for 2 h open to air. The resultant mixture was filtered through a silica gel pad and concentrated in vacuo. Flash chromatography of the residue (5% EtOAc in hexane) afforded ***c*-3a** (two isomers) and ***t*-3a** as colorless oils.
***c*-3a** (β-NO_2): R_f = 0.66 (20% EtOAc in hexane). IR (CH_2Cl_2): 3551, 2943, 2873, 1606, 1546, 1453, 1378 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.17 (dd, *J* = 12.9, 3.7 Hz, 1 H), 2.92 (s, 1 H), 2.41 (qd, *J* = 13.0, 4.6 Hz, 1 H), 2.01–1.94 (m, 1 H), 1.88 (td, *J* = 13.8, 4.9 Hz, 1 H), 1.79 (td, *J* = 13.9, 4.4 Hz, 1 H), 1.75–1.64 (m, 3 H), 1.64–1.55 (m, 3 H), 1.55–1.43 (m, 1 H), 1.35 (dt, *J* = 14.0, 3.1 Hz, 1 H), 1.17–1.10 (m, 2 H), 1.08 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 87.3, 73.6, 39.0, 34.8, 32.9, 31.9, 27.3, 23.2, 22.1, 20.8, 19.7. MS (EI, 20 eV): *m/z* (%) = 213 (2) [M^+], 196 (1), 167 (7), 149 (100). HRMS (EI): *m/z* calcd for $C_{11}H_{19}NO_3$ [M^+]: 213.1365; found: 213.1353.
***c*-3a** (α-NO_2): R_f = 0.57 (20% EtOAc in hexane). IR (CH_2Cl_2): 3563, 2937, 2869, 1606, 1545, 1453, 1370 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.73 (dd, *J* = 12.0, 5.3 Hz, 1 H), 2.77 (s, 1 H), 2.10 (m, 1 H), 2.06 (qd, *J* = 13.4, 5.0 Hz, 1 H), 1.96 (td, *J* = 13.7, 4.6 Hz, 1 H), 1.87–1.53 (m, 6 H), 1.49–1.38 (m, 2 H), 1.22–1.12 (m, 2 H), 1.09 (dm, *J* = 13.7 Hz, 1 H), 1.08 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 90.8, 74.7, 39.2, 36.3, 32.3, 27.5, 27.2, 22.4, 21.1, 21.0, 19.3. MS (EI, 20 eV): *m/z* (%) = 196 (0.2) [M^+ – OH], 167 (17), 149 (100). HRMS (EI): *m/z* calcd for $C_{11}H_{18}NO_2$ [M^+ – OH]: 196.1338; found: 196.1326.
***t*-3a**: R_f = 0.71 (20% EtOAc in hexane). IR (CH_2Cl_2): 3559, 2948, 2869, 1542, 1483, 1446, 1373 cm^{-1}. ^1H NMR (500

MHz, $CDCl_3$): δ = 4.68 (dd, *J* = 12.8, 4.1 Hz, 1 H), 2.60 (s, 1 H), 2.47 (qd, *J* = 12.6, 7.1 Hz, 1 H), 2.01–1.96 (m, 1 H), 1.91–1.78 (m, 2 H), 1.78–1.73 (m, 1 H), 1.73–1.66 (m, 2 H), 1.66–1.60 (m, 1 H), 1.59–1.46 (m, 3 H), 1.25–1.20 (m, 1 H), 1.07–1.03 (m, 1 H), 1.03 (s, 3 H), 0.98 (dt, *J* = 13.1, 3.3 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 90.0, 73.0, 38.2, 34.9, 32.9, 29.6, 27.2, 20.6, 20.3, 19.5, 19.1. MS (EI, 20 eV): *m/z* (%) = 196 (0.2) [M^+ – OH], 167 (8), 149 (100). HRMS (EI): *m/z* calcd for $C_{11}H_{18}NO_2$ [M^+ – OH]: 196.1338; found: 196.1302. The relative stereochemistries of ***c*-3a** (β-NO_2), ***c*-3a** (α-NO_2), ***t*-3a** (β-NO_2), and all other cyclized compounds **3** were determined by 2-D NOE spectral correlations.

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(21) The different ratios of diastereomeric products obtained under the two reaction conditions (Table 1, entry 2 and Equation 2) implies that ***t*-3b** is the kinetic product and that the thermodynamic energies of ***c*-3b** and ***t*-3b** are comparable. That ***t*-3b** is the kinetic product was further confirmed by being the only product isolated when the reduction of **2b** at –40 °C was quenched after 15 min. The optimized configurations of ***t*-3b** and ***c*-3b** by DFT calculations using the B3LYP/6-31G (d) model showed that ***t*-3b** was thermodynamically more stable than ***c*-3b** by 2.1 kcal/mol.

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