USEFUL EXTENSIONS OF THE HENRY REACTION: EXPEDITIOUS ROUTES TO NITROALKANES AND NITROALKENES IN AQUEOUS MEDIA

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GRAPHICAL ABSTRACT

Abstract The products of the Henry nitroaldol reaction from nitromethane and several aldehydes were reduced to the corresponding nitroalkanes with (n-Bu)₃SnH in water under microwave irradiation (80 °C/10 min), or dehydrated to the corresponding nitroalkenes with K₂CO₃ in water (generally 0–5 °C/20 min). Both “one-pot” reactions occur in excellent yields across a range of aliphatic and aromatic (including heteroaromatic) substrates. It seems likely that the deoxygenation of the nitroaldols occurs via coordination of an oxygen atom of the nitro group with a tin atom, which facilitates hydride delivery in the transition state. The elimination of water from the nitroaldols in mild base is likely driven by the stability of the conjugated nitroalkene products. The elimination required workup with 2 N HCl, which likely displaces a nitroalkane-nitroalkene equilibrium towards the latter. These extensions of the Henry reaction lead to products not easily obtained otherwise.

Keywords Aldol; aqueous conditions; dehydration; deoxygenation; Henry; nitromethane; tin hydride

INTRODUCTION

The Henry nitroaldol reaction is a most useful variant of the classical aldol condensation.[1–5] In its most general definition, it involves the condensation of an aliphatic nitro compound (1) with an aldehyde (2) and leads to the formation of β-nitroalcohols (3, Scheme 1). Wide scope and generally excellent yields characterize the reaction, which represents one of the few definitive approaches to aliphatic nitro derivatives.
The scope of the Henry reaction has been considerably expanded by the development of methods for the dehydration of the nitroalcohol adducts to the corresponding nitroalkenes, which are valuable synthetic intermediates that undergo a variety of nucleophilic and cycloaddition reactions. Furthermore, the ease of reduction of the nitro group to the corresponding amine offers a plethora of possibilities for the synthesis of diverse nitrogen-containing compounds, generally renowned for their biological activities.

Interestingly, however, current methodology has certain limitations in terms of both scope and operational ease. Thus, the Henry reaction is still performed with nitromethane or its immediate congeners, essentially because the higher nitroalkanes are not easily accessed. Also, although the β-nitroalcohol adducts may be dehydrated to the corresponding nitroalkenes by several methods, the competing reversal of the Henry reaction itself is a problem. It was thus of interest to develop methods for further extending the scope of the synthetically valuable Henry reaction.

In particular, we were interested in methods for the reductive removal of the nitro and hydroxyl functionalities, under conditions as mild and environmentally friendly as possible. It is noteworthy that the Henry reaction itself can be performed in aqueous media, which opens a door to green approaches to aliphatic nitro compounds and beyond (cf. above brief discussion of the scope of the reaction). This work carries these ideas forward, and described below are extensions of the Henry reaction that constitute very useful additions to current methodology. (In the event, we also discovered a remarkably easy method for the dehydration of the nitroalcohol adducts.)

RESULTS AND DISCUSSION

Reductive Cleavage of the Hydroxyl Group in Henry Adducts to Form Nitroalkanes

The higher homologs of nitromethane and nitroethane, the two most readily available nitroalkanes, are not easily accessed. Essentially, this is because the alkylation of their nitronate anions leads to mixtures of C and O alkylation products.[6] An interesting approach to this methodological limitation is based on the deoxygenation of the β-nitroalcohol adducts of the Henry reaction. Current methodology effects this transformation in two steps, via initial dehydration to the nitroalkene, followed by its reduction.[7] Several methods are available for the first elimination step, and the second reduction step is typically performed with sodium borohydride. A recently reported one-step method involves reduction of β-nitroalcohols with Me₃SiH/trifluoroacetic acid (TFA) but works only in the presence of activating
substituents.\[8\] Thus, there was a need for a direct one-step method of wide scope, preferably carried out in aqueous media, for this transformation.

Initially, we were interested in extending the scope of the reduction of the Henry adducts by tributyltin hydride. These are known to lead to denitration in organic solvents,\[9\] forming the corresponding alcohols in good yields. During studies aimed at extending this reaction to aqueous media, we discovered that deoxygenation—rather than denitration—occurred under microwave irradiation in water. Thus, 2-nitro-1-phenylethanol (4\textsubscript{a}) reacted with 1.5 equivalents of \(n\)-Bu\textsubscript{3}SnH in water, under microwave irradiation over 10 m at 80 °C, forming 2-phenyl-1-nitroethane (5\textsubscript{a}) in 96% yield (Scheme 2; Table 1, entry 1). The reaction was of wide scope, with a large variety of Henry adducts derived from nitromethane undergoing the reaction, generally in excellent yields (Table 1). There appears to be a moderate steric effect in the reaction, as reflected in the relatively lower yields in the case of substrates with ortho substituted aryl rings adjacent to the hydroxyl group being reduced (entries 6, 8, and 10). Also, alkyl substituents on the carbon atom bearing the nitro group apparently suppressed the reaction, again presumably because of a steric effect (entries 18 and 19).

Also, rather interestingly, the yields in the case of 5\textsubscript{a} were found to be lower in the presence of the radical initiators azo-bis-isobutyronitrile and dibenzyl peroxide (AIBN and DBP, respectively). Similar results were obtained in the presence of the radical scavengers 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) and galvinoxyl. A possible explanation for these results could be that these additives lead to the slow degradation of tributyltin hydride under the conditions employed. However, the fact that 5\textsubscript{a} is still formed in relatively good yields in their presence likely indicates an ionic—rather than a radical—mechanism for this reaction.

We thus propose the hydride transfer mechanism shown in Scheme 2. In this, the reaction is mediated by prior coordination between an oxygen atom of the neighboring nitro group, leading to a six-membered cyclic transition state. (The coordination would increase the nucleophilicity of the hydride moiety being transferred.)

The reduction of conjugated nitroalkenes with tributyltin hydride has been reported previously in organic media, apparently under neutral radical-free conditions.\[10\] However, we are not aware of the one-step reduction of Henry adducts with tin hydride reagents having been reported. Also, control experiments indicated

\begin{center}
\textbf{Scheme 2.} Microwave-assisted deoxygenation of Henry adducts (4) with tri-\(n\)-butyltin hydride under aqueous conditions, to form the nitroalkanes 5 via transition state I.
\end{center}
Table 1. Dehydroxylation of 2-nitroalcohols (4) to nitroalkanes (5) (cf. Scheme 2)

| Entry | Substrate (4a–s) | Product (5a–s) | Reaction time (min) | Isolated yield (%) |
|-------|------------------|----------------|---------------------|--------------------|
| 1     | ![4a](image)     | 5a             | 10                  | 96                 |
| 2     | ![4b](image)     | 5b             | 12                  | 89                 |
| 3     | ![4c](image)     | 5c             | 10                  | 86                 |
| 4     | ![4d](image)     | 5d             | 15                  | 78                 |
| 5     | ![4e](image)     | 5e             | 20                  | 72                 |
| 6     | ![4f](image)     | 5f             | 90                  | —                  |
| 7     | ![4g](image)     | 5g             | 8                   | 88                 |

(Continued)
| Entry | Substrate (4a–s) | Product (5a–s) | Reaction time (min) | Isolated yield (%) |
|-------|------------------|----------------|---------------------|-------------------|
| 8     | ![Image](image1.png) | 5h             | 8                   | 58                |
| 9     | ![Image](image2.png) | 5i             | 6                   | 86                |
| 10    | ![Image](image3.png) | 5j             | 6                   | 63                |
| 11    | ![Image](image4.png) | 5k             | 5                   | 85                |
| 12    | ![Image](image5.png) | 5l             | 5                   | 92                |
| 13    | ![Image](image6.png) | 5m             | 5                   | 90                |
| 14    | ![Image](image7.png) | 5n             | 5                   | 95                |
| 15    | ![Image](image8.png) | 5o             | 5                   | 93                |
| 16    | ![Image](image9.png) | 5p             | 5                   | 95                |
that this reduction of the nitro alcohols 4 to the nitroalkanes 5 was not mediated by the corresponding nitroalkenes 6 (cf. Scheme 3). Thus, 6 were not formed from 4 under microwave irradiation in water.

### Dehydration of Henry Adducts to Form Nitroalkenes

The elimination of water from the Henry adducts has previously been accomplished by several procedures. These generally involve the prior activation of the hydroxyl group followed by a base-induced elimination process. Reagents employed include MsCl-Et3N,\(^{10b,11}\) Ac₂O-AcONa,\(^{12}\) Ph₃P-CCl₄-Et₃N,\(^{13}\) TFA-Et₃N,\(^{14}\) catalytic piperidine-molecular sieves,\(^{15}\) N,N'‐dicyclohexylcarbodiimide (DCC),\(^{16}\) phthalic anhydride,\(^{17}\) P₂O₅,\(^{18}\) Al₂O₃,\(^{19}\) pivaloyl chloride,\(^{20}\) SmI₂,\(^{21}\) etc. Recently, heterogeneous catalysts such as functionalized silica,\(^{22}\) zeolite,\(^{23}\) and MCM-41\(^{24}\) have been reported to effect the dehydration of 2-nitroalcohols to

![Dehydration of Henry Adducts to Form Nitroalkenes](image)

| Entry | Substrate (4a–s) | Product (5a–s) | Reaction time (min) | Isolated yield (%) |
|-------|-----------------|----------------|---------------------|-------------------|
| 17    |                 | 5q             | 10                  | 85                |
| 18    |                 | 5r             | 90                  | —                 |
| 19    |                 | 5s             | 90                  | —                 |

**Scheme 3.** Dehydration of Henry adducts (4) under mild aqueous basic conditions, to furnish the (E)-nitroalkenes 6 (the mechanism shown does not indicate possible reversibility).
| Entry | Substrate (4a–q) | Reaction time (min) | Nitroolefin (6a–q) | Isolated yield (%) |
|-------|------------------|---------------------|-------------------|-------------------|
| 1     | ![](image1.png)  | 15                  | 6a                | 96                |
| 2     | ![](image2.png)  | 20                  | 6b                | 78                |
| 3     | ![](image3.png)  | 15                  | 6c                | 87                |
| 4     | ![](image4.png)  | 25                  | 6d                | 74                |
| 5     | ![](image5.png)  | 30                  | 6e                | 65                |
| 6     | ![](image6.png)  | 30                  | 6f                | 68                |
| 7     | ![](image7.png)  | 5                   | 6i                | 67                |

(Continued)
nitroalkenes. Generally, however, these methods employ relatively expensive and toxic reagents and furnish moderate to good yields of the nitroalkene products.

In the course of studies with Henry adducts, we discovered that their dehydration could be accomplished under remarkably mild aqueous conditions. Thus, 2-nitro-1-phenylethanol (4a) was treated with potassium carbonate in water at 0–5°C over 20 min; acidification with 2 N HCl and workup furnished 2-phenyl-1-nitroethylene in 96% yield. The procedure could be extended to a wide range of nitroethanols 4 as shown in Table 2, with the corresponding nitroalkenes (6) being isolated in excellent yields.

### Table 2. Continued

| Entry | Substrate (4a–q) | Reaction time (min) | Nitroolefin (6a–q) | Isolated yield (%) |
|-------|------------------|---------------------|-------------------|-------------------|
| 8     | ![4k](image1)    | 15                  | 6k                | 93                |
| 9     | ![4l](image2)    | 15                  | 6l                | 82                |
| 10    | ![4m](image3)    | 15                  | 6m                | 85                |
| 11    | ![4n](image4)    | 25                  | 6n                | 83                |
| 12    | ![4o](image5)    | 20                  | 6o                | 86                |
| 13    | ![4p](image6)    | 20                  | 6p                | 88                |
| 14    | ![4q](image7)    | 30                  | 6q                | 85                |
Interestingly, no nitroalkene was recovered in the absence of the final acidification step. It seems likely that in the basic medium employed, an equilibrium is established between nitroalcohol 4 and nitroalkene 6 that is displaced toward 6 upon neutralization (cf. Scheme 3). (Acidification presumably neutralizes hydroxide ion, the most basic component in the mixture.) The proposed mechanism is supported by the fact that the α-proton of a nitro compound has a closely similar pKₐ to that of the carbonate ion (~10).[25]

It is particularly remarkable that a dehydration reaction occurs expeditiously in water. However, it is apparently driven by the stability of the conjugated nitroalkene product in a neutral medium. Also, performing the reaction at greater pH (with NaOH rather than K₂CO₃) apparently led to the retro-Henry reaction (reversal of the reaction in Scheme 1), as seen from the spectra of the reaction mixture. With K₂CO₃ only traces of the retro-Henry reaction products were observed, the resulting aldehyde (2) being removed during workup by washing with NaHSO₃ solution.

CONCLUSIONS

New and improved methods for the conversion of several Henry nitroaldol adducts to the corresponding nitroalkanes and nitroalkenes have been developed in aqueous media. (The adducts were obtained from nitromethane and a variety of aldehydes.) The deoxygenation to the nitroalkanes was effected with tributyltin hydride under microwave conditions, whereas the elimination to the nitroalkenes was effected with potassium carbonate. These straightforward procedures, effected by easily available reagents, are characterized by short reaction times and simple workup and purification. The aqueous media employed indicate their utility as environmentally compatible “green” methodologies. These unprecedented one-step conversions extend the scope of the Henry reaction and add significantly to current methodologies.

EXPERIMENTAL

The following instruments were employed: CEM Discover Focused Microwave Synthesis System (microwave synthesizer), Perkin-Elmer 410 (FTIR), Bruker AV-400 (NMR), Micromass Q-TOF AMPS MA X 10/6A (HRMS), Stuart SMP10 (melting point), and Büchi Rotavapor R-200 (rotary evaporator). Further experimental details, including full characterization data for all reported compounds, are given in the accompanying supplementary information.

**General Procedure for Dehydroxylation of 2-Nitroalcohols 4**

A heterogeneous mixture of 2-nitroalcohol (4, 1.2 mmol), n-Bu₃SnH (0.38 g, 1.3 mmol), and deionized water (2 mL) in a 10-mL microwave vessel fitted with a septum was irradiated in a microwave oven at 300 W and 80 °C for 5–20 min. The cooled mixture was worked up by extraction with ether, and the extracts were washed with water and dried (Na₂SO₄). The resulting crude product was purified chromatographically on silica gel (eluent: 5:95 ethyl acetate–hexane). The pure nitroalkane products (5) were identified spectroscopically. Thus, infrared (IR)
showed the absence of the OH stretching band at $\sim 3500 \text{ cm}^{-1}$, and $^1H$ NMR the absence of the $–\text{OCH}$ resonance in the region $\delta 4.1–6.2$, both present in 4. The $\text{CH}$ resonance $\alpha$ to NO$_2$ was present in both 4 and 5 at $\delta 4.5$.

**General Procedure for Dehydration of 2-Nitroalcohols 4**

A heterogeneous mixture of 2-nitroalcohol (4, 1.2 mmol) and deionized water (2 mL) at 5–10°C, was treated portionwise with powdered K$_2$CO$_3$ (0.18 g, 1.3 mmol). The mixture was stirred at 5–10°C until it turned homogeneous. The reaction mixture (at 5–10°C) was acidified with 2 N HCl to pH 6 and extracted with ether. The extracts were washed with NaHSO$_3$ solution and water to remove traces of aldehyde (deriving from a competing retro-Henry reaction). Removal of the solvent in vacuo furnished the corresponding (E)-nitroalkene (6), found to be homogeneous by thin-layer chromatography (TLC) and characterized spectroscopically. The disappearance of the hydroxyl group from 4 was deduced as indicated in the previous procedure. In the NMR, the twin alkene proton resonances were observed the region $\delta 6.9–8.0$, generally as an AB spin system; a relatively large $J$ value of $\sim 13 \text{ Hz}$ indicates that the $E$ isomer of 6 was formed in the reaction.

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**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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