Reaction of Henry adducts with aqueous sodium borohydride

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Cogent Chemistry (2015), 1: 1080210
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Abstract: A sequential retro-Henry reduction reaction of 2-nitroalcohols to corresponding alcohols in aqueous sodium borohydride solution is described. The method has large substrate scope and furnished corresponding alcohols in 76–99% yield in 5–30 min at room temperature. The utility of reaction in chemoselective reduction of α,β-unsaturated aldehydes and ring opening of cyclic tert-β-nitroalcohols to open-chain sec-nitroalcohols are also demonstrated. Experimental studies on the mechanism of reaction showed that sodium borohydride may be reducing the aldehyde formed during the reaction, via retro-Henry reaction of 2-nitroalcohols catalysed by in situ-generated “base”, to alcohol.

Subjects: Applied & Industrial Chemistry; Materials Chemistry; Natural Products; Organic Chemistry

Keywords: 2-nitro alcohols; borohydride; retro-Henry; reduction; C–C bond cleavage

1. Introduction

Henry adducts (1, 2-nitroalcohols) are the products of the Henry reaction, the reaction of carbonyl compound with nitroalkane in the presence of a catalytic base (Henry, 1895). Henry adducts are extensively used reaction intermediates in pharmaceuticals, natural product synthesis and in fine chemicals industry (Ballini, 1991; Heffner, Jiang, & Joullie, 1992; Kisanga & Verkade, 1999; Mikite, Jakucs, Kis-Tamás, Darvas, & Lopata, 1982; Rosini, 1991; Sakanaka, Ohmori, Kozaki, & Suami, 1986; Suami, Sasai, &...
Matsuno, 1983). They can be transformed into other useful functionalities such as nitroalkenes, nitroalkanes, aminoalcohols, α-nitroketones, α-hydroxyketones, alcohols and β-hydroxycarbonyl compounds (Luzzio, 2001).

The reactions of 1 are generally carried out in the absence of moisture because the traces of water present in the reaction pot can reduce productivity of the reaction by directing the retro-Henry reaction: conversion of 1 to aldehyde and nitroalkane (Li & Corey, 2009). Even though the retro-Henry reaction is an inherent drawback of Henry reaction, the reaction is used for the resolution of racemic 2-nitroalcohols and enantioselective organocatalytic synthesis of 5-nitro-pent-2-enoates (Gao, Ren, Siau, & Wang, 2011; Yuryev, Briechle, Gruber-Khadjawi, Griengl, & Liese, 2010). The key intermediates essential for the synthesis of pharmaceutically and biologically important compounds such as R-(+)-α-lipoic acid and ω-amino acids were achieved by retro-Henry reaction of cyclic 2-nitroalcohols (Ballini, Papa, & Abate, 1999; Bezbarua, Saikia, Barua, Kalita, & Ghosh, 1996). Also, a short synthesis of (±)-phoracantholide involved the retro-Henry reaction of cyclic 2-nitroalcohols followed by the reduction of initially formed aldehyde (Scheme 1) (Saikia et al., 1996).

The above strategies use hazardous reagents (CuSO4-SiO2-benzene, NaOH-PTC-H2O, etc.) for retro-Henry reaction under reflux conditions for longer reaction time. Therefore, development of a sustainable strategy for the retro-Henry reaction and reduction of 1 seems important. Herein, an efficient condition for “one-pot” sequential retro-Henry reduction reactions of 1 in aqueous sodium borohydride at room temperature is reported. In this, synthesis of alcohols and nitroalkanes from acyclic 2-nitroalcohols (Scheme 2) and nitroalcohols from cyclic 2-nitroalcohols (Scheme 3) is described. During the reaction, 1 underwent cleavage of C1–C2 bond followed by the addition of hydrogen to C1 and C2 carbon atoms.
2. Results and discussion

When 2-nitro-1-phenylethanol (1a, 0.5 g, 3.0 mmol) was reacted with NaBH₄ (85 mg, 2.3 mmol) in water (2.5 mL) at r.t., quantitative yield of benzyl alcohol (2a, >99%) was formed in 10 min (Scheme 2). At least three equivalents of NaBH₄ (2.3 mmol) were required for the completion of reaction. Quantities lower than three equivalents of NaBH₄ resulted in the formation of a mixture of aldehyde and alcohol due to incomplete reduction of aldehyde, as shown by TLC and ¹H NMR. The formed products were pure in the case of water as solvent as compared to other solvent mediums (organic solvents or aqueous-organic solvent mixture) and also their yield.

Range of 2-nitroalcohols have undergone the reaction and furnished corresponding alcohols and nitroalkanes in good to excellent yield in few minutes (Table 1). 1 bearing electron-withdrawing aryls took lesser time as compared to electron-donating aryls for the transformation (1a–d, 1i–1l). Even heteroaryl and aliphatic groups containing 2-nitroalcohols have reacted under these reaction conditions (1e–f). Generally, unsaturated alcohols from α,β-unsaturated aldehydes were achieved by chemoselective 1,2-reduction at low temperatures using hydride reducing agents or by hydrogenation (Sun et al., 2014; Uysal, Aksu, & Oksal, 2013). But the present methodology produces unsaturated alcohols at room temperature from 1 in quantitative yields (1g–h).

| Entry | Substrate (1a–l) | Product (2a–l) | Reaction time (min) | Isolated yield (%) |
|-------|-----------------|----------------|--------------------|--------------------|
| 1     | ![1a](image)     | 2a             | 10                 | >99                |
| 2     | ![1b](image)     | 2b             | 20                 | 83                 |
| 3     | ![1c](image)     | 2c             | 10                 | 80                 |
| 4     | ![1d](image)     | 2d             | 8                  | 95                 |
| 5     | ![1e](image)     | 2e             | 5                  | 84                 |

(Continued)
## Table 1. (Continued)

| Entry | Substrate (1a–l) | Product (2a–l) | Reaction time (min) | Isolated yield (%) |
|-------|------------------|----------------|---------------------|--------------------|
| 6     | 1f               | 2f             | 10                  | 85                 |
| 7     | 1g               | 2g             | 8                   | 93                 |
| 8     | 1h               | 2h             | 10                  | >99                |
| 9     | 1i               | 2i             | 15                  | >99                |
| 10    | 1j               | 2j             | 15                  | 92                 |
| 11a   | 1k               | 2k             | 20                  | 78                 |
| 12b   | 1l               | 2l             | 15                  | 85                 |

*a* Isolated yield of nitromethyl benzene (3k) was 75%.

*b* Isolated yield of (2-nitroethyl)benzene (3l) was 83%.
Also, the ring opening of cyclic tert-β-nitroalcohols (1m–p) was achieved using this strategy in highly efficient manner (Scheme 3, Table 2). These products were used as intermediates for the synthesis of (±)-tridecan-12-olide and (±)-9-tetradecanolide (Bez, Saikia, Kalita, Bezbarua, & Barua, 1998).

On coming to the mechanism of reaction of Henry adducts with aqueous NaBH₄, there are two possibilities (Scheme 4). First involves the direct attack of hydride ion on to the carbon atom containing hydroxyl group of a six-membered borane complex of 2-nitroalcohol, A. Second is retro-Henry reaction of borane complex of 2-nitroalcohol, B, followed by the reduction of aldehyde.

Usually, the retro-Henry reaction of cyclic 2-nitroalcohols requires high temperature with a strong base, sodium hydroxide. (Ballini et al., 1999; Camps, Muñoz-Torrero, & Muñoz-Torrero, 1995; Martinelli, Gugliotta, & Tei, 2012) Surprisingly, when 1 (both acyclic and cyclic) was added to an aqueous solution of NaBH₄, the retro-Henry occurred at room temperature. In a control experiment, when i (0.5 g) was allowed to react at r.t. in borate buffer solution at pH 9.0 (5 mL), >99% of benzaldehyde was formed in 15 min. However, when the above reaction was carried out in 2N sodium hydroxide solution, only 65%

| Entry | Substrate (1m–p) | Product (4m–p) | Reaction time (min) | Isolated yield (%) |
|-------|------------------|----------------|---------------------|--------------------|
| 13    | ![1m](image1)    | 4m             | 20                  | 78                 |
| 14    | ![1n](image2)    | 4n             | 20                  | 86                 |
| 15    | ![1o](image3)    | 4o             | 20                  | 76                 |
| 16    | ![1p](image4)    | 4p             | 25                  | 82                 |

Scheme 4. Transition states A and B.
of benzaldehyde was formed in 2 h may be because the reactants and products were in equilibrium. These experiments support the fact that borane co-ordinated to 2-nitroalcohol in a complex B would weaken the C1-C2 bond and lead the retro-Henry reaction to completion.

Furthermore, when 1i (1 equiv) was reacted with NaBH4 (3 equiv) in water, it was observed that the pH of the reaction mixture quickly increases from 7 to 12 during the progress of reaction may be because of the conversion of NaBH4 to sodium metaborate via NaOH in the presence of water (Kojima, Kawai, Nakanishi, & Matsumoto, 2004; Lo, Karan, & Davis, 2007). This in situ-generated base was responsible for triggering the retro-Henry reaction. Moreover, when 1i (1 equiv) was reacted with NaBH4 (3 equiv) in D2O, formation of C6H5CH2OD and CH3CHDNO2 was observed in 1H NMR. However, when only one equivalent of NaBH4 in D2O was used to react with 1i (1 equiv), formation of a mixture of C6H5CH2OD, CH3CHDNO2, benzaldehyde and deuterated 1i was confirmed in 1H NMR. The presence of both aldehyde and alcohol in the reaction mixture in case of lower equivalents of NaBH4 supported the fact that the reaction occurs in two steps: retro-Henry reaction and reduction (see Supplementary material).

Based on the above experimental results, the possible mechanism of the reaction is proposed as shown in Scheme 5. At first, NaBH4 reacts with water and forms sodium hydroxide, borane and hydrogen. Now, 1 can co-ordinate with borane to form complex B, in which the Lewis acidic borane co-ordinated to the oxygen atom of nitro group weakens the C1-C2 bond. Here, the water molecules may form strong hydrogen bonding with heteroatoms of B. This might initiate the retro-Henry reaction in the presence of in situ-generated base, sodium hydroxide, to form aldehyde and boron nitronate, E. The boron nitronate E reduces aldehyde to primary alcohol and forms another boron nitronate F, which can reduce one more molecule of 1. The mechanism shows that the reaction requires slightly more than two equivalents of NaBH4 for completion of the reaction. Alternatively, it is also possible that the presence of excess NaBH4 can reduce the initially formed aldehyde simultaneously.

3. Conclusions
Developing benign synthetic methodologies is an increasing prerequisite in current industrial research (Anastas, 2010; Dunn, Wells, & Williams, 2010). In conclusion, a simple mild-aqueous condition for sequential retro-Henry reduction reactions of Henry adducts has been developed. The method utilizes environmentally benign conditions such as water as a reaction medium, has wide substrate scope and furnishes excellent yields in short reaction time. Also, the scope of the methodology in chemoselective reduction of α,β-unsaturated aldehydes and ring opening of cyclic tert-β-nitroalcohols has been described.
Mechanistic investigations on the reactions have showed that the reaction proceeds via retro-Henry reduction pathway and not by intramolecular hydride transfer to a six-membered borane complex of 2-nitroalcohol.

4. Experimental

4.1. General procedure for reduction of 2-nitroalcohols

To a heterogeneous mixture of 1 (3.0 mmol, 1 equiv) and water (5 mL) in flask at room temperature, powdered NaBH₄ (2.3 mmol, 3 equiv) was slowly added and stirred until 1 disappeared in the reaction mixture by TLC. After the reaction, the reaction mixture was diluted with 2N hydrochloric acid (10 mL) and extracted with ether (2 × 20 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated to yield a crude alcohol as product. The other products nitromethane and nitroethane were removed during work-up. The spectral data showed that the compounds were sufficiently pure and did not require any further purification. Thus, IR showed the shift of OH stretching band present at ~3,500 cm⁻¹ in 1 to ~3,450–3,350 cm⁻¹ on converting to alcohol. ¹H NMR showed the absence of the –OCH resonance in the region δ 4.1–6.2 and the appearance of –OCH₃ resonance in the region δ 3.6–5.0.

In the case 2-nitroalcohols 1k–p, crude products were purified chromatographically on silica gel (eluent: 15:85 ethyl acetate-hexane). ¹H NMR showed that the CH₃ resonance α to NO₂ was present at ~δ 4.4 and –OCH resonance was found at δ 3.4–4.3.

Supplementary material for this article can be accessed here.

Acknowledgements

Annadka Shrinidhi thanks Mr. Srinivasa Murthy, Department of Organic Chemistry, Indian Institute of Science (Bangalore) for helping carrying out the NMR experiments. Also, he is grateful to the Council of Scientific & Industrial Research for their generous fellowship support.

Funding

The author received no direct funding for this research.

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Citation information

Cite this article as: Reaction of Henry adducts with aqueous sodium borohydride, Annadka Shrinidhi, Cogent Chemistry (2015), 1: 1080210.

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