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Protic additives in aprotic solvent: a tool to improve sodium borohydride reductions of C–C bonds

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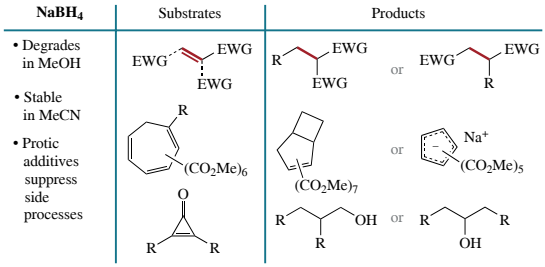
This study explores the reduction of electrophilic carbon–carbon double bonds using sodium borohydride in aqueous acetonitrile to effectively protonate reactive intermediate enolate anions, thereby mitigating unwanted polymerization processes. The reduction of strong Michael acceptors leads to the corresponding saturated ('dihydro') analogues. In cases of electron-poor cycloheptatrienes and proaromatic cyclopropenones the initial reduction is followed by either ring-contraction or ring-opening, respectively.

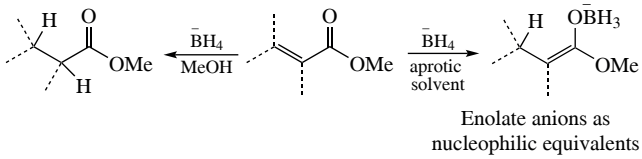


Keywords: sodium borohydride, reduction, aromaticity, Favorskii reaction, Nazarov reaction, electrocyclic reactions, transition state aromaticity, olefins, cycloheptatrienes, cyclopropenones.

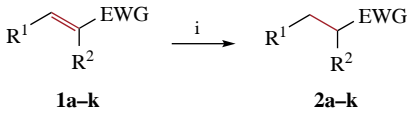
Sodium borohydride $NaBH_4$ has been a cornerstone in the field of reduction chemistry since its introduction in the 1940s.[1] The common protocol includes the use of alcohol solvents such as methanol and ethanol, which are believed to generate effective reducing agents, alkoxyborohydride anions, through the partial quenching of $NaBH_4$ with alcohols.[2] However, the utility of $NaBH_4$ is often hampered by its rapid solvolysis in these alcohols, necessitating the use of up to ten equivalents of $NaBH_4$ and additional heating for the reduction of esters under standard conditions.[3] The presence of neighbouring assisting groups in esters has been shown to significantly improve reagent utilization,[4–7] similar results for esters can be achieved in the presence of a strong base.[8] While $NaBH_4$ is capable of reducing carbon–carbon double bonds in the presence of transition metal compounds, these reactions tend to behave more like hydrogenation processes, commonly resulting in a lack of selectivity between electron-rich and electron-poor double bonds. This is due to the formation of metal borides through the reaction of $NaBH_4$ with transition metal salts and hydrogen from the interaction of $NaBH_4$ with alcohols.[9–13]

The moving from protic to aprotic solvents has proven beneficial in the reduction of carbonyl compounds,[14] alkyl[15] and aryl[16] halides and carboxylic acid derivatives.[17] In the latter case, aprotic solvents allow for elevated reaction temperatures without significant decomposition of $NaBH_4$, a limitation often encountered with alcohols. Instances of nucleophilic reductions of carbon–carbon double bonds in Michael acceptors using $NaBH_4$ remain limited to highly activated substrates such as nitro- and dicyanoalkenes.[18–24] Examples of the reduction of Knoevenagel products formed from malonates in either alcohols at reduced temperature[25,26] or in a methanol–acetonitrile mixture are also known.[27] In this article, we present a comprehensive study on the application of $NaBH_4$ for the reduction of activated electrophilic carbon–carbon double bonds, including those within cycloheptatriene rings. Additionally, we investigate a unique case involving the reduction of a single carbon–carbon bond, contributing to the understanding and utility of $NaBH_4$ in organic synthesis.

The main challenge of the utilization of aprotic solvents for the reduction of electrophilic carbon–carbon double bonds with $NaBH_4$ consists in the following. Alcohols not only form reactive alkoxyborohydrides but are also responsible for proton exchange reactions to form a reduced single bond. Conversely, in the absence of a protic component the reduction of a Michael acceptor should produce a nucleophilic equivalent of enolate anion instead (Scheme 1), which apparently induces polymerization of the substrate. Therefore, we suggested the use of a mixture of acetonitrile and a protic additive to inhibit the side polymerization processes. We found that the use of 5% of protic additives (CF_3CH_2OH, H_2O and MeOH) did not induce their reaction with $NaBH_4$. This was confirmed by the presence of solely borohydride ions in an NMR spectrum of $NaBH_4$ in a 5% solution of water in acetonitrile (see Online Supplementary Materials). Experiments with the reduction of dimethyl fumarate **1a** to form dimethyl succinate **2a** have shown that the addition of 5% of water in acetonitrile improved the reaction outcome and reduced the polymerization process relative to dry acetonitrile. The use of trifluoroethanol provided similar results as water while methanol underwent its addition to the Michael acceptor. The use of acetic acid as an additive gave no reduction but an

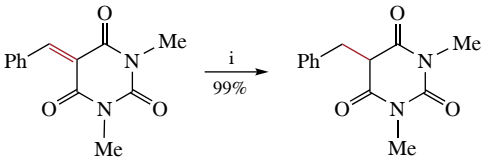


Scheme 1



1a–k **2a–k**

a EWG = R^1 = CO_2Me, R^2 = H, 85%
b EWG = R^1 = CO_2Et, R^2 = H, 93%
c EWG = R^1 = CO_2Pr^i, R^2 = H, 87%
d EWG = R^1 = CO_2Me, R^2 = CH_2CO_2Me, 39%
e EWG = R^2 = CO_2Me, R^1 = Cy, 58%
f EWG = R^2 = CO_2Me, R^1 = Ph, 72%
g EWG = R^2 = CO_2Me, R^1 = 4-$MeOC_6H_4$, 73%
h EWG = R^2 = CO_2Me, R^1 = 4-NCC_6H_4, 90%
i EWG = R^2 = CO_2Me, R^1 = 2,6-$Cl_2C_6H_3$, 78%
j EWG = R^2 = CN, R^1 = Ph, 73%
k EWG = R^2 = CN, R^1 = 4-$O_2NC_6H_4$, 60%
EWG = CO_2Me, R^1 = Ph, R^2 = H: no reaction



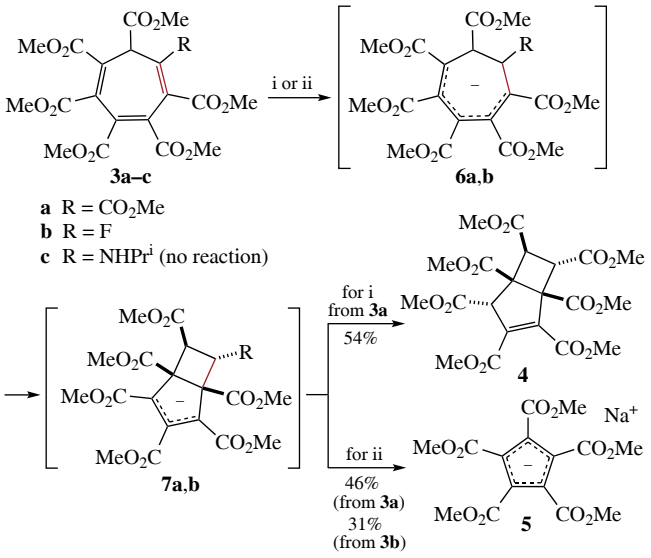
1l **2l**

Scheme 2 *Reagents and conditions*: i, $NaBH_4$, MeCN/H_2O (95 : 5), room temperature.

intense hydrogen evolution occurred instead (see Online Supplementary Materials).

We implemented our protocol for the reduction of activated double bonds on a series of alkenes **1a–l** featuring either vicinal or heminal electron-withdrawing groups (Scheme 2). The corresponding saturated products **2a–l** were obtained in moderate to excellent yields, all the functional groups remaining intact. However, methyl cinnamate bearing only one electron-withdrawing group was not reduced at room temperature.

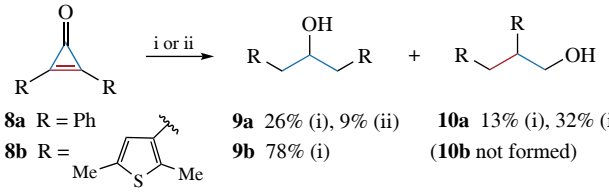
In our previous works we explored the reduction of hepta(methoxycarbonyl)cycloheptatriene **3a** with $NaBH_4$ in propan-2-ol to obtain bicycloheptene **4** at room temperature[28] or sodium cyclopentadienide **5** upon heating (Scheme 3).[29] In this work, we demonstrate that our aqueous acetonitrile system can effectively produce bicycloheptene **4** (conditions i) while heating in pure acetonitrile facilitates the formation of cyclopentadienide **5** (conditions ii). The observed lower yields compared to previous studies may be attributed to the small-scale experiments of the current study. In attempts to expand the scope of cyclopentadienyl anion derivatives we found that fluorine analogue **3b**[30] on heating



3a–c

a R = CO_2Me
b R = F
c R = $NHPr^i$ (no reaction)

Scheme 3 *Reagents and conditions*: i, $NaBH_4$, MeCN/H_2O (95 : 5), room temperature, 1 h; ii, $NaBH_4$, MeCN, reflux, 5 h.



8a R = Ph
8b R =

9a 26% (i), 9% (ii)
9b 78% (i)

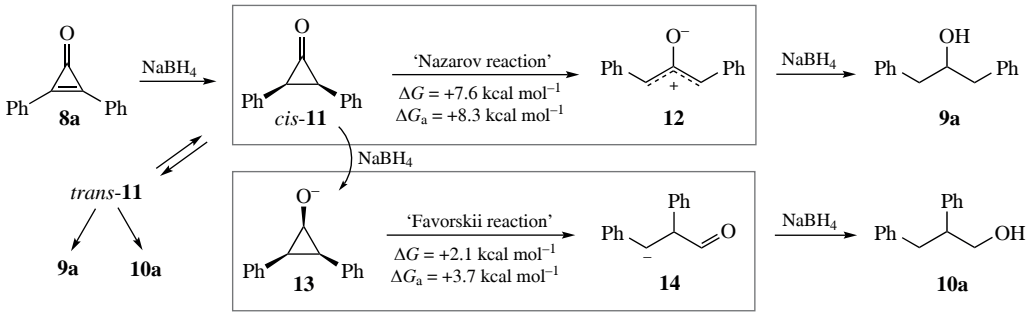
10a 13% (i), 32% (ii)
(**10b** not formed)

Scheme 4 *Reagents and conditions*: i, $NaBH_4$, MeOH, room temperature, 1 h; ii, the same, in MeCN/H_2O. For **9a/10a**, NMR yields are given.

with $NaBH_4$ in dry MeCN was converted into the same product **5** as that derived from **3a**. This outcome can be explained by the enhanced steric accessibility of the fluorinated carbon atom within the seven-membered ring, which promotes the reduction of the fluorinated double bond, leading to anion **6b**. This anion subsequently undergoes electrocyclic ring contraction to yield species **7b** followed by a retro-[2+2]-cycloaddition, ultimately resulting in the product **5** devoid of fluorine. In contrast, aminocycloheptatriene **3c**[30] exhibited no reactivity, likely due to both steric and electronic factors.

Cyclopropenones are highly strained cyclic compounds of proaromatic nature, as evidenced by a $NICS(1)_{zz}$ value of –9 for compound **8a** (Scheme 4), which contributes to their significant polarization (other NICS values are given in the Online Supplementary Materials). Consequently, these compounds can be considered highly activated electrophilic alkenes. To date, there has been only one documented instance of the reduction of a cyclopropenone derivative using lithium aluminum hydride[31] to afford the corresponding cyclopropanol. Here we investigated the reactivity of cyclopropenones towards $NaBH_4$ and revealed formal reduction of single carbon–carbon bonds. In methanol, diphenylcyclopropenone **8a** yielded a mixture of isomeric acyclic alcohols **9a** (major) and **10a** (minor), while bis(dimethylthienyl)cyclopropenol **8b** exclusively produced isomer **9b** (see Scheme 4). The use of aqueous acetonitrile reversed the selectivity of reduction of **8a** and increased the total yield. Known alcohols **9a** and **10a** were not isolated pure and were identified by NMR spectra of the worked-up reaction mixtures.

Concerning the mechanism for the formation of products **9a**,**b**, we suggest that the key step involves an electrocyclic ring-opening of cyclopropanones generated through the reduction of cyclopropenones. This reaction yields so-called oxyallyl[32] intermediates, which are subsequently reduced into propan-2-ols. Quantum chemical calculations using the revDSD-PBEP86(D4)/aug-cc-pVTZ//r^2SCAN-3c level of theory indicate that for diphenylcyclopropenone **8a** the key ring-opening of *cis*-cyclopropanone *cis*-**11** exhibits a modest increase in free energy of only 3.5 kcal mol^{-1} with an activation free energy of 6.9 kcal mol^{-1} (Scheme 5). Notably, *trans*-**11** is unlikely to undergo a ring-opening reaction as the activation free energy would be 23.2 kcal mol^{-1} with an increase in free energy of 15.9 kcal mol^{-1}; however, it is anticipated that these two isomers can readily interconvert. The stability of this Nazarov-type transition state may be attributed to strain relief and its aromatic characteristics, which was supported by the negative $NICS(1)_{zz}$ values from the two sides of the three-membered ring (–6 and –10) in the ring-opening of *cis*-**11**. The formation of side product **10a** within the reduction of compound **8a** can be attributed to a Favorskii-type ring-opening reaction[33] involving cyclopropylate anion **13** with an intermediary formation of carbanion **14**. Quantum chemical calculations revealed an extremely low barrier of 3.7 kcal mol^{-1} for the ring opening of all-*cis*-**13** with a free energy increase of 2.1 kcal mol^{-1}; however, other isomers can also yield product **14** (see Online Supplementary Materials). The increased Favorskii-type direction in aqueous acetonitrile is due



Scheme 5

to highest reactivity of cyclopropanone **11** towards borohydride anion relative to methoxyborohydride anion formed in methanol. The reduction of bis(dimethylthienyl) derivative **8b** does not yield product **10b** due to steric hindrance from the bulky dimethylthienyl groups, which impede the reduction of the carbonyl group in the corresponding cyclopropanone intermediate.

In conclusion, we investigated the reduction of electrophilic carbon–carbon bonds in an aqueous acetonitrile system using sodium borohydride. Our findings indicate that the presence of 5% water significantly mitigates side oligomerization processes of activated alkenes. We successfully applied this protocol to electrophilic cycloheptatrienes, leading to the formation of a bicycloheptene derivative and penta(methoxycarbonyl)cyclopentadienyl anion. However, our results suggest that alternative cyclopentadienyl-anion derivatives are unlikely to be accessible through this method. Furthermore, we demonstrated that cyclopropenones exhibit considerable activation due to their aromatic character, and their reduction is accompanied by 2π-Nazarov or Favorskii-type ring-opening reactions, resulting in the formation of the corresponding alcohols.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7763.

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