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Reduction Over Condensation of Carbonyl Compounds Through a Transient Hemiaminal Intermediate Using Hydrazine

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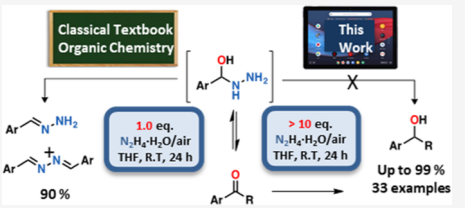
ABSTRACT: Reduction of carbonyl moieties to the corresponding alcohol using simply hydrazine hydrate has been considerably unfeasible until now due to the well-known condensation reaction. However, herein, we report that using an excess of 20-fold equivalents, the reduction proceeds in excellent yields. ^{1}H NMR study of the reaction and density functional theory (DFT) calculations indicate that the final fate of the hemiaminal intermediate is crucial to obtain the alcohol or the hydrazone.



INTRODUCTION

The use of hydrazine hydrate as a hydrogen donor for unsaturated organic compounds has been known for decades.[1,2] There are numerous experimentally and theoretically based arguments indicating that the active hydrogen transfer reagent is not hydrazine, but diimide (NH═NH).[2,3] The most widespread application has been found in the saturation of olefins or multiple carbon−carbon bonds.[4] Also, nitro groups have been reduced to the corresponding amines but only in the presence of metal catalysts, such as Pd, Ni, and Ru.[2,5,6]Aldehydes and ketones can be converted into alkanes by the use of hydrazine under harsh Wolff−Kishner conditions (high temperature, solid KOH),[7,8] where the corresponding alcohol has been reported as a byproduct.[9] Although hydrazine is considered as a reducing agent, the reduction of aldehydes or ketones to the corresponding alcohols has largely been considered unfeasible due to the rapid condensation reactions.[10] However, it is noteworthy that this reduction has been observed using diimide, but from a source other than hydrazine, and, to the best of our knowledge, limited to only two examples. Thus, to exclude the condensation reaction of the supernucleophile hydrazine with the carbonyl group, the application of metal azodicarboxylate (metal = Na+ or K+) has been suggested.[11,12] The unstable hydrogen donor diimide is released in situ by the effect of water or acid. Alternatively, the decomposition of anthracene-9,10-diimine in boiling ethanol has been suggested as a source for diimide.[13] Classical textbook chemistry teaches that the condensation reaction of aldehyde (or ketones) with hydrazine hydrate[14] proceeds through an intermediate tetrahedral hemiaminal, but this is normally not observed. Since the initial pioneering work of Jencks and Cordes, other groups have demonstrated that the rate-limiting step in the imines, oximes, and hydrazones is the dehydration of the corresponding carbinolamine.[15] In this sense, the identification of the rate-determining step plays a crucial role in providing an in-depth understanding of the mechanism of a particular reaction. However, identification of molecules that sometimes last for only a fraction of seconds constitutes a significant challenge due to their poor stability. On this basis, Fujita has remarkably been able to trap the elusive intermediate of a Schiff base condensation reaction using a porous coordination network, highlighting the importance of such short-lived species.[16] Taking inspiration from this reasoning, in this study, we disclose, for the first time, the reduction of aromatic carbonyl moieties in the presence of an excess of hydrazine hydrate to the corresponding alcohols. To validate this methodology, several aldehydes, ketones, and benzophenones were reduced. Additionally, ^{1}H NMR and density functional theory (DFT) studies were performed, exploring the relative thermodynamics of the intermediates and products to explain this unusual transformation. In comparison to other reducing agents, e.g., molecular hydrogen or complex metal hydrides, hydrazine offers interesting advantages.[17,18] Thus, besides the desired molecular hydrogen in the optimal case, only molecular nitrogen and water are formed during the transfer hydrogenation as harmless byproducts. Moreover, the application of hydrazine hydrate does not require special pressure vessels or safety measurements and it can be purchased in huge quantities at low prices.

RESULTS AND DISCUSSION

In our seminal attempts, we explored the reduction of *p*-bromo benzaldehyde as a benchmark system in different solvents

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using an excess of hydrazine hydrate of 20-fold equivalents as well as the effect of temperature (Table 1, entries 1−8). In a first trial, 2-propanol was used and the corresponding hydrazone **2a** as the main product and traces of the azine **3a** were formed.[19]

Table 1. Screening of Reaction Conditions for the Reduction of *p*-Br-Benzaldehyde with an Excess of $N_2H_4 \cdot H_2O$[a,b]

entry	solvent	$N_2H_4 \cdot H_2O$ equiv	T [°C]	conv. [%]	yield [%]
1	2-PrOH	20	22	>99	14
2	EtOH	20	22	>99	11
3	CH_3CN	20	22	>99	23
4	THF	20	22	>99	87
5	dioxane	20	22	>99	31
6	acetone	20	22	32	7
7	THF	20	50	>99	18
8	THF	20	5	69	8

[a]Reaction conditions: 0.5 mmol of *p*-Br-benzaldehyde and 0.5 mL of $N_2H_4 \cdot H_2O$ (10 mmol) in 4.5 mL of solvent under air for 24 h. [b]Conversion and yields were determined by gas chromatography (GC) with decane as the internal standard.

Unexpectedly, also 14% of *p*-bromobenzyl alcohol **4a** was detected (entry 1). In ethanol as well as acetonitrile, acetone, and dioxane, **4a** was formed, albeit in similarly low quantities (entries 2−3 and 5−6), with the lowest conversion and yield observed in acetone. However, we were surprised to note that up to 83% of **4a** was obtained in THF (tetrahydrofuran) under otherwise identical conditions (entry 4). The influence of the reaction temperature was also investigated (entries 7−8). By lowering the temperature to 5 °C or increasing the temperature to 50 °C, the yield of **4a** decreased to 8 and 18%, respectively. Once we established THF as the solvent of choice, we investigated the effect of using an increasing amount of hydrazine hydrate from one equivalent. Thus, we found a remarkable dependence on the product of the reaction relative to the hydrazine concentration. When 1 equivalent of hydrazine hydrate was used, the condensation products **2a** and **3a** were predominantly formed in 90% yield as a mixture. However, using more than 10-fold excess of hydrazine, up to 83% of benzyl alcohol was obtained (Figure 1).

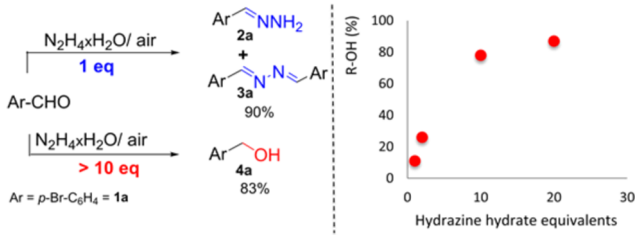

Figure 1. Distribution products according to the substrate/hydrazine ratio.

To demonstrate the applicability of our new synthetic methodology, the scope of the reaction including several aromatic aldehydes, ketones, and benzophenones with varied substitution patterns was explored (Table 2). Although no clear trend due to the electronic nature of the substituents was established, good to excellent yields were reached with substrates bearing a halogen- or electron-withdrawing group, e.g., up to 93% for **4j**. A similar result was observed with mono- or di-ortho/meta-substituted aldehydes bearing electron donor groups (**4g**). However, when these groups were in the para position, lower yields were obtained (**4n**) and the corresponding hydrazones or azines were observed as major byproducts. Interestingly, independent of the electronic properties of the substituent, meta-substituted substrates were efficiently reduced (**4f**, **4k**, **4m**). The new hydrogenation methodology was also efficient for the reduction of aromatic ketones. A similar trend to the substituted aldehydes was observed regarding the substitution pattern. High conversions along with high yields were obtained, e.g., up to 99% for **5m**. In general, the reaction of aromatic ketones containing halogen- or electron-withdrawing groups was favored, giving moderate to excellent yields (57−99%). The reaction was less efficient with para-substituted ketones (**5l**). Also, in the case of benzophenone derivatives **6a−d**, the reduction was successfully carried out (80−90%). Other functionalities sensitive to reduction such as nitro and cyano groups were tolerated under the reaction conditions. Even substrates containing halogens did not undergo dehalogenation, except for **4q**, where a small amount of the dehalogenated product was observed. To increase the synthetic potential of this methodology, we performed scaling up to 2.7 mmol, yielding **5c** in 71% of isolated yield of the desired alcohol.

Considering the novelty and potential of this methodology, we were interested in investigating the course of the reaction. Since hydrazones are easily formed,[20] we thought of the back-reaction to the aldehyde, which would be later reduced to the alcohol. The proposal of the hydrazone as the intermediate necessarily involves discovering the oxygen source. It is known that in the oxidation reaction of hydrazine hydrate in the presence of air or pure O_2, hydrogen peroxide is formed.[21] Thus, molecular oxygen or hydrogen peroxide might promote the back-reaction.[22] In this sense, we found that the treatment of hydrazone **2a** with small amounts of H_2O_2 and daylight decreased its concentration dramatically within a short time. Under these conditions, besides the relevant aldehyde **1a**, azine **3a** was formed. Higher concentrations of H_2O_2 (20 equiv) considerably increased the formation of aldehyde **1a**. Based on this evidence, hydrazone **2a** and azine **3a** were prepared and separately subjected to the reaction instead of *p*-bromo benzaldehyde. After 24 h, alcohol **4a** was obtained only in 19 and 13% yields, respectively. To test the role of the oxygen, the reaction was carried out under anaerobic conditions. As a result, no benzyl alcohol (**4a**) was formed, highlighting the necessity of oxygen in the reaction. Nevertheless, its participation does not explain the fact that a lower yield was obtained using **2a** or **3a**. We speculate that a reactive intermediate species is formed before the hydrazone. The reversibility of such a process has already been a subject of investigation.[23] In that work, the authors indicate that at a high hydrazine concentration, equilibrium with a hemiaminal species is observed. Accordingly, this delicate equilibrium might be an important factor to consider in our reaction.

To gain insights into the mechanism, a density functional theory (DFT) study was carried out. In addition to the extensive literature describing the formation of diimide as a reducing agent generated by reacting a large excess of hydrazine hydrate under aerobic conditions, we computed the free Gibbs energy for its formation. Our calculation predicts that diimide generation is thermodynamically favored by −31.6 kcal/mol and nonviable in the absence of oxygen. In

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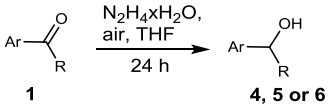
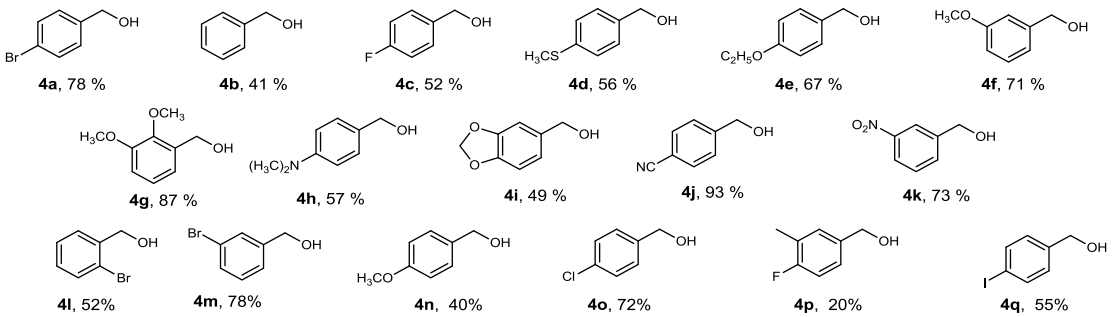
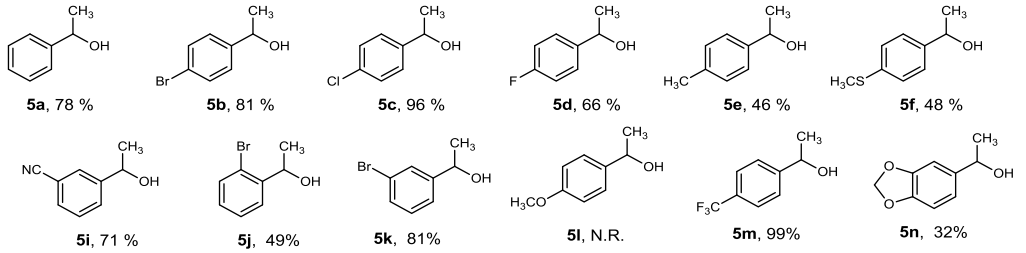
Table 2. Transfer Hydrogenation of Carbonyl Compounds with Hydrazine Hydrate[a,b]



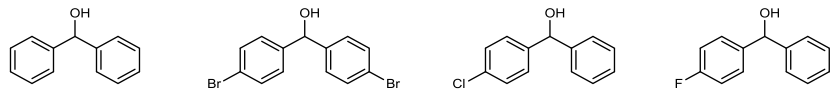
Aldehydes



Acetophenones



Benzophenones



[a]Reaction conditions: 0.5 mmol of substrate and 0.5 mL of $N_2H_4.H_2O$ (10 mmol) in 4.5 mL of solvent under air for 24 h. [b]Isolated yields. N.R. = no reaction.

this manner, we proposed a 1,2-hydrogenation process between diimide and the aldehyde through a cyclic transition state (TS) structure releasing nitrogen as a byproduct (Figure 2). The computed activation Gibbs free energy for this step (10.2 kcal/mol) strongly suggests that this process can occur under mild conditions. The exergonicity of this reaction is predicted to be very large (ΔGrxn = −60.3 kcal/mol). On the other hand, the nucleophilic attack of hydrazine onto the carbonyl compound gives the zwitterionic intermediate **int-1**. The computed activation barrier for this N−C bond-forming step is predicted to be extremely fast ($\Delta G^{\ddagger}$ = 4.9 kcal/mol). The subsequent proton transfer step leading to the hemiaminal intermediate **int-2** has an overall barrier of 7.7 kcal/mol and it is exergonic by −6.0 kcal/mol, contrary to the endergonic processes associated with short-lived species.[13] Nonetheless, Fujita and co-workers pointed out that the free-energy surfaces for these reactions are strongly dependent on the molecular environment. Indeed, our computation reveals that the Gibbs free energy changes from −6.0 kcal/mol for a hydrogen-bound hemiaminal intermediate to −1.8 kcal/mol for a "naked" intermediate (Supporting Information (SI)). These results prompt us to postulate **int-2** as the key intermediate of our reaction and not hydrazone **2** as we had previously proposed. In such a scenario, a reversibility process from **int-2** to **1** would be facilitated under our reaction conditions, which would be reduced by the formed diimide. Otherwise, at the final stage, the hemiaminal intermediate would collapse, releasing a water molecule to give the hydrazone **2** as the final product. This process has an overall activation barrier of 25.2 kcal/mol, qualifying as the rate-determining step, in good agreement with the seminal findings of Cordes and Jencks. This proposal is interesting because although diimide has been reported as the reducing agent of carbonyl compounds, it has also been highlighted that polar double bonds are reduced slowly or are completely inert toward diimide.[2a,b]

Since we have no experimental evidence of the hemiaminal species, we envisioned that following the reaction by ^{1}H NMR spectroscopy with THF-d_8 as the solvent and deuterated hydrazine as the reagent could validate our hypothesis, since the reaction would proceed much slower due to an isotopic effect and the transient hemiaminal intermediate could be detected (Figure 3). At the beginning of the reaction, disappearance of the signals at δ 7.78 indicates that the concentration of the starting aldehyde **1a** dropped almost to zero but not due to hydrazone formation but the hemiaminal intermediate, which is quickly formed in agreement with our computed energy profile. As the reaction progresses, the singlet at δ 5.27, characterizing the proton of the CH unit of the hemiaminal, disappears. Interestingly, since the reaction was carried out at 10 °C, to detect the hemiaminal, the singlet at δ

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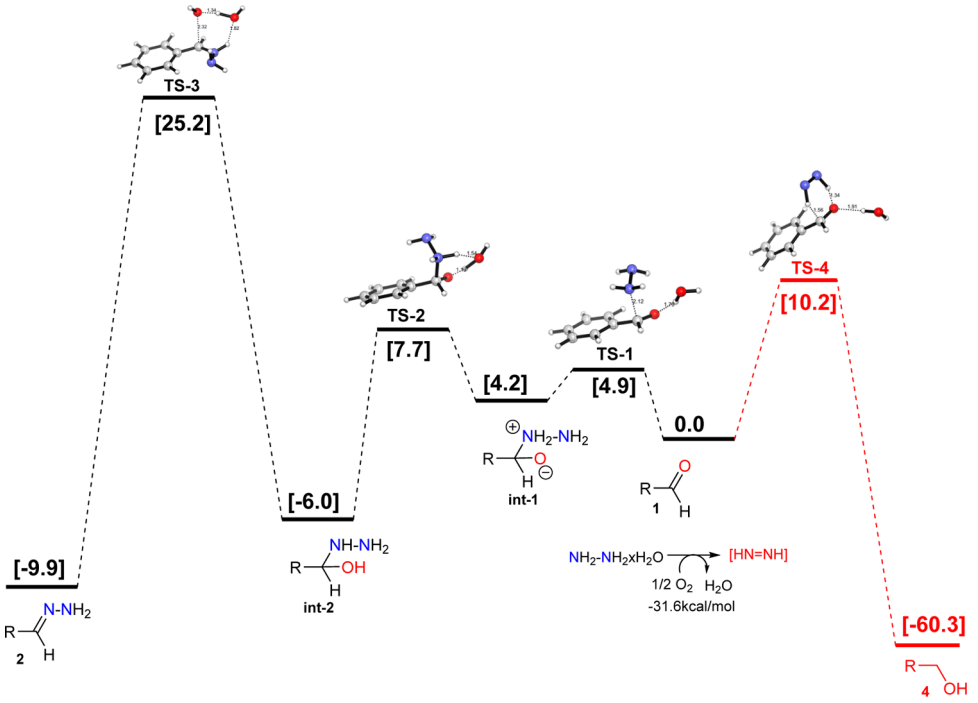

Figure 2. Computed Gibbs energy profile, in kcal/mol, and transition states (TS) for the reaction between benzaldehyde (square brackets) and hydrazine hydrate.

7.63 corresponding to the CH═NND$_2$ proton of the hydrazone **2a** as well as the aromatic doublet at δ 7.28 (J = 8.83 Hz) from the benzyl alcohol **4a** are simultaneously generated. The expected triplet for the signal H$_e$ corresponding to the reduced product is not well resolved and appears as a singlet at δ 4.53. Moreover, despite the excess hydrazine used, after 8 h of reaction, a small resonance characterizing the formyl proton at δ 9.95 remains constant and completely disappears only after 24 h. At 24 h, the concentration of the hydrazone and the alcohol is the same (50% ^{1}H NMR yield), in agreement with the temperature dependence shown in Table 1. At this time, a signal corresponding to a monodeuterated water (HOD) or to the hydroxy group due to a deuterium exchange appears at δ 4.43.

■ CONCLUSIONS

In conclusion, we have found a new and entirely unexpected one-pot production of alcohols from the corresponding aromatic aldehydes and ketones, respectively, using simply hydrazine hydrate as the hydrogen source. We have rationalized these results in terms of reversibility, and the thermodynamic energy profile of the reaction paths was calculated. From this study, a hemiaminal species was postulated as a key intermediate of the reaction. Following the reaction by ^{1}H NMR spectroscopy, we were able to observe this species, confirming our hypothesis. With this finding, we have broadened the utility of hydrazine as a reducing agent not only for olefins but also for aromatic carbonyl compounds.

■ EXPERIMENTAL SECTION

All reagents were used as received without further purification. ^{1}H NMR spectra were recorded at room temperature on a Bruker 400.13 MHz. Gas chromatography measurements were performed on a Shimadzu GC-2014 Plus with an Rtx-5 column (30 m × 0.25 mm × 0.25 μm). Mass spectra were recorded on a Varian 450 GC triple quadrupole coupled to a Varian 320-MS mass spectrometer equipped with an electronic impact source (EI). The anaerobic reaction was run under an argon atmosphere using Schlenk techniques. Compounds **2a** and **3a** were synthesized following the reported procedures.[24,25]

General Procedure for the Synthesis of Standard Alcohols for GC Analysis. To a solution of the carbonyl compound (2.5 mmol) in THF (15 mL) under stirring was added NaBH$_4$ (1.3 mmol, 0.049 g) portionwise at 0 °C. The temperature of the reaction was allowed to increase until room temperature, and the reaction mixture was stirred overnight. Water (10 mL) was added dropwise and the solvent was evaporated. The aqueous solution was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and finally, the solvent was evaporated under vacuum. The product was used without further purification.

General Procedure for the Reduction of 1a Under Anaerobic Conditions. An NMR tube was dried and purged with argon in a Kontes NMR tube-sealing manifold and 0.168 mmol of *p*-bromo benzaldehyde (31 mg) was added. THF-d_8 (1.0 mL) and 10 equiv of hydrazine hydrate (83 mg) were added under an argon atmosphere by a syringe. The NMR tube was sealed by a stopper and sealing tape and shaken. After different time intervals, NMR spectra were recorded and between the measurements, the tube was shaken again for one minute. The same reaction was carried out in a small Schlenk tube (10 mL) with continuous stirring under an argon atmosphere. After 6 and 34 h, respectively, a sample was taken under anaerobic conditions for the NMR investigation.

General Procedure for the Reaction of 2a with Hydrogen Peroxide. Hydrazone **2a** (0.25 mmol) was placed into a 20 mL glass screw-thread septa vial and dissolved in 3.9 mL of THF, and 0.10 mL of H$_2$O$_2$ (30% aq) was added. The reaction mixture was stirred at room temperature and analyzed by gas chromatography taking an aliquot of 0.1 mL from the vial and diluted in 0.9 mL of THF at reaction times of 1 min and 2 h.

General Procedure for the Synthesis of Compounds 4a-q, 5a-n, and 6a-d with Hydrazine Hydrate. To a solution of the corresponding carbonyl compound (0.5 mmol), in 4.5 mL of THF into a glass screw-thread septa vial was added 0.5 mL of hydrazine hydrate (10 mmol). The reaction mixture was stirred at room temperature under air for 24 h. After the reaction time, the solvent

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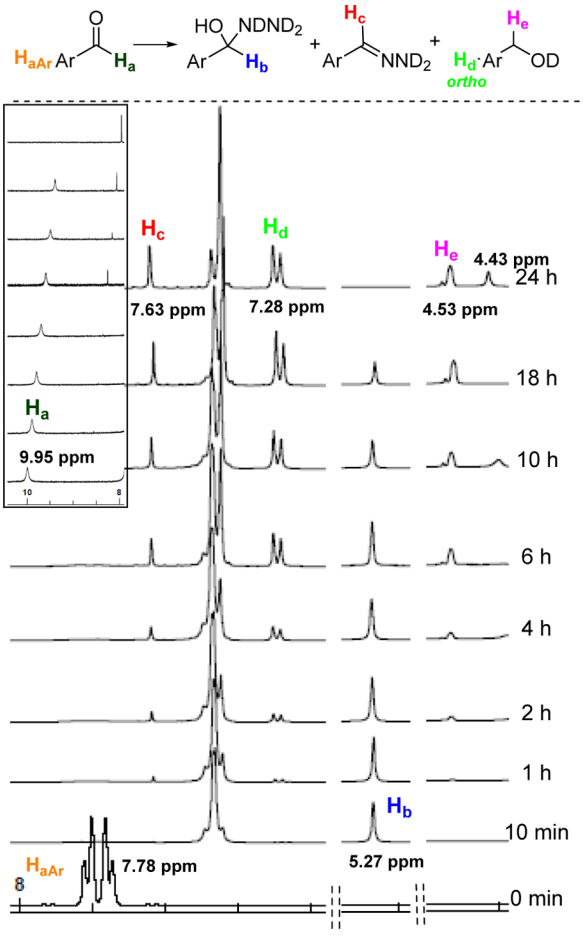

Figure 3. Progress of alcohol formation through the hemiaminal intermediate followed by ^{1}H NMR. Ar = *p*-Br-benzaldehyde. Reaction conditions: 0.5 mmol of *p*-Br-benzaldehyde and 0.5 mL of $N_2D_4{\cdot}D_2O$ (10 mmol) in 4.5 mL of THF-d_8 under air for 24 h at 10 °C.

was evaporated under reduced pressure and the crude mixture was subjected to ^{1}H NMR analysis without further purification. For the quantification of the products, the crude was purified by column chromatography eluted with a mixture of ethyl acetate/*n*-hexane. The purity and additional identification of all products were confirmed by GC and GC−MS with the NIST library and compared with those reported in the literature.[26] The reaction on a large scale (2.7 mmoles) furnished **5c** in 71% yield (415 mg).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01212.

A copy of ^{1}H NMR for compounds **1a**, **2a**, **3a**, and **4a** and a copy of GC and GC−MS chromatograms for compounds **4a**−**4q**, **5a**−**5n**, and **6a**−**6d** are available (PDF)

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Notes

The authors declare no competing financial interest.

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