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Hydrogenolysis of geminal diazides

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ABSTRACT

The complete hydrogenolysis of compounds containing the geminal diazido functionality is described. Using hydrogen over palladium on charcoal, the diazides are reduced, and primary amines are obtained. For example, aminomalonates and glycines are generated in a straightforward manner. A protocol that provides direct access to acetylated amines derived from 2-amino-1,3-diketones in good to excellent yields, *via* hydrogenation in the presence of acetic anhydride, is also presented.

Introduction

The chemistry of compounds containing geminal diazido groups has been rarely studied: until recently, only a rather small number of compounds with this motif have been reported in the literature,[1,2] and their synthesis was mostly limited to classical substitution reactions with dihalides and azide anions.[3] With regard to the reactivity of geminal diazides, the research has focused on their thermolysis[4] and photochemical degradation.[5]

Over the last couple of years, we have shown in a number of publications how geminal diazides derived from 1,3-dicarbonyl compounds can be easily obtained: for example, the use of iodine and sodium azide in aqueous DMSO allowed the smooth conversion of a broad range of 1,3-dicarbonyl compounds **1** into their diazido congeners **2** (Scheme 1a).[6] Other groups have also reported valuable methods for the synthesis of geminal diazides, thus expanding the scope of readily available compounds containing the diazido functionality.[7] With powerful methods in hand, we then started to systematically uncover the reactivity of geminal diazido compounds, mainly distant from thermolysis and photolysis reactions.[8,9] These diazido compounds are potentially hazardous, and gaining knowledge on their controlled reactivity is important when new methods with diazido intermediates are envisioned.[10] Herein, we report the hydrogenolysis of geminal diazides **2** derived from 1,3-dicarbonyls (Scheme 1b). It was shown that, under standard hydrogenation conditions, primary amines **3** were formed in a straightforward manner.

Results and discussion

We conducted our initial study with the diazide derived from *N*,*N*′-dibenzyl malonamide (**2a**), a compound that was found to be reasonably stable towards both thermal decomposition and harsh hydrolysis conditions. As shown in Table 1, all hydrogenation attempts resulted in the rapid formation of primary amine **3a**. For example, use of the $AlCl_3$-Fe couple in aqueous ethanol led to the corresponding amine, albeit with low conversion.[11] The reduction with $InCl_3$ and Et_3SiH in acetonitrile gave full conversion and quantitative yields of the amine; however, we were not able to purify the product upon work-up.[12] The pure amine **3a** was obtained in 70% yield employing ammonium formate and zinc in methanol.[13] Significantly better results were obtained with hydrogen over palladium on charcoal:[14] complete hydrogenolysis of diazide **2a** took place in methanol and in aqueous methanol, at room temperature and atmospheric hydrogen pressure. When performing the reaction in CH_2Cl_2 at room temperature, 100 psi of hydrogen were optimal to achieve full conversion of the starting diazide into the desired amine **3a**.

Although not evidenced by experimental data, we speculate that the initially formed diamino compound **A** is converted into imine **B** upon the loss of ammonia. Alternatively, azide intermediate **A**′ may rapidly convert into **B** *via* expulsion of the azide anion. Further reduction with hydrogen may then give rise to amine **3**. Notably, in the presence of Lindlar catalyst, the formation of imine **4a** was observed, and the isolation of this intermediate en route to amine **3a** was possible in 35% yield (Scheme 2).

Despite its novelty, the hydrogenolysis of geminal diazides may have limited applications. Running the reactions on small scales is

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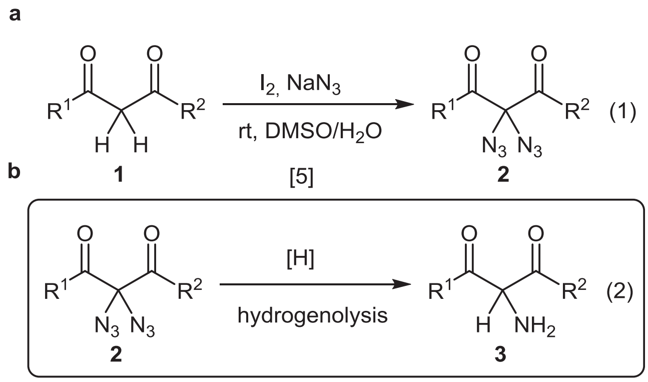
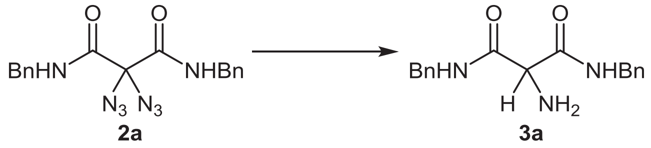
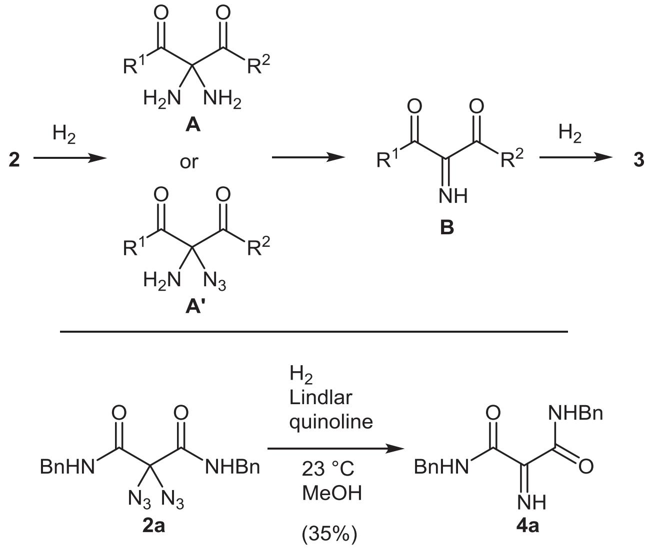


Scheme 1. Synthesis[5] and hydrogenation of geminal diazides.

Table 1
Hydrogenolysis of diazide **2a**.



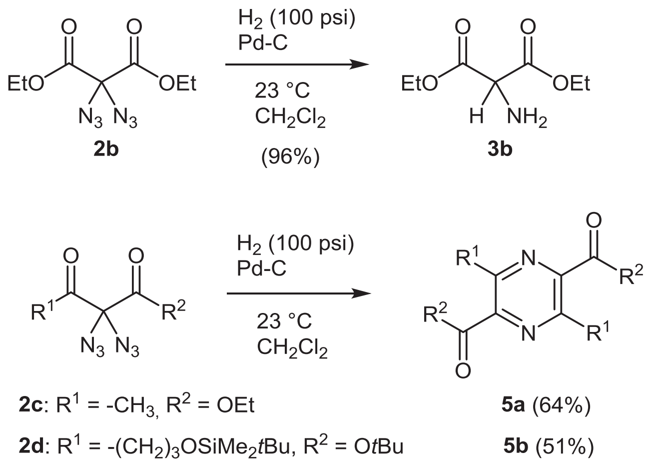
Entry	Conditions	Yield of **3a** [%]
1	Fe, $AlCl_3$ EtOH-H_2O, 23 °C	9
2	$InCl_3$, Et_3SiH MeCN, 23 °C	Quant. yield
3	Zn, $H_4N^+HCO_2^-$ MeOH, 23 °C	70
4	H_2 (1 atm), 15 mol% Pd-C MeOH-H_2O, 23 °C	91
5	H_2 (1 atm), 15 mol% Pd-C dry MeOH, 23 °C	96
6	H_2 (100 psi), 15 mol% Pd-C CH_2Cl_2, 23 °C	91



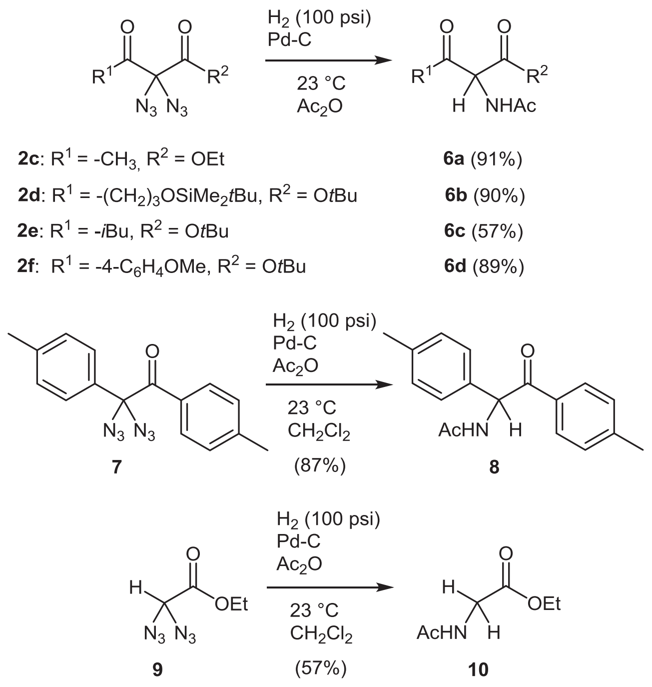
Scheme 2. Proposed mechanism.

strictly advised since the diazido starting materials are potentially explosive compounds. However, the standard method for the production of compounds containing the amino functionality between two carbonyls, such as **3**, is reduction of the corresponding oximes (e.g., *via* the reduction of 2-hydroxylimino 1,3-dicarbonyls); and the generation of oximes also has some safety issues.[15] A more recent alternative is the direct amination of 1,3-dicarbonyls.[16] Yet the direct α-amination of malonates is barely feasible, in contrast to the smooth amination of 1,3-diketones and 3-oxo esters. We point out that our diazidation-hydrogenation sequence represents a simple method to accomplish the synthesis of aminated malonates. Under standard hydrogenation conditions using 15 mol% of palladium on charcoal with 100 psi of hydrogen in CH_2Cl_2 at room temperature, diazides derived from malonates smoothly gave the corresponding amines, as exemplified by the conversion of diester **2b** (Scheme 3). In this particular case, CH_2Cl_2 was the solvent of choice since the alternative use of methanol led to transesterification. When reducing diazides from 3-oxo esters (e.g., **2c** and **2d**), the corresponding pyrazine heterocycles **5a** and **5b** were generally obtained as the main products through classical dimerization in moderate yields.[17]

We then focused on a more practical reaction, with the goal of supressing the pyrazine-forming dimerization during the reduction of diazides derived from 3-oxo esters.[18] To this end, the hydro-



Scheme 3. Hydrogenolysis of diazides.



Scheme 4. Hydrogenolysis of diazides in the presence of acetic anhydride.

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genation was performed in acetic anhydride at room temperature, and the acetylated amines **6a**–**6d** were obtained. As shown in Scheme 4, this method is a useful tool for the synthesis of *N*-acetylated 3-oxo 2-amino esters, and the yields were typically high. Additionally, the reduction of other diazido compounds not possessing a 1,3-dicarbonyl motif was feasible. For example, diazide **7** with a single carbonyl group in proximity to the diazido unit gave the acetylated amine **8** in good yields while the reduction of diazidated ethyl acetate **9** resulted in the formation of the acetylated glycine **10**.

Conclusion

In conclusion, we have shown that readily available geminal diazides undergo complete hydrogenolysis when treated with hydrogen in the presence of palladium on charcoal. The yields for formation of the corresponding amino-containing products are typically high. The straightforward reduction of diazides **2**, which are directly accessed from 1,3-dicarbonyl compounds through simple diazidation, may attract particular interest. This reaction provides amines with the amino group positioned between the two carbonyls and, thus, represents a possible alternative to the classical synthesis of those amines *via* reduction of the corresponding oximes.[15] We hope that this reaction will further enrich the knowledge on the diverse chemistry of geminal diazido compounds.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.066.

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