Accepted Manuscript

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| PII: DOI: Reference: | S0040-4039(17)31453-3 https://doi.org/10.1016/j.tetlet.2017.11.039 TETL 49482 |
|----------------------------|---|
| To appear in: | Tetrahedron Letters |
| Received Date: | 6 October 2017 |

Revised Date:13 November 2017Accepted Date:17 November 2017



Please cite this article as: Llabres-Campaner, P.J., Woodbridge-Ortega, P., Ballesteros-Garrido, R., Ballesteros, R., Abarca, B., Heterogeneous Borrowing Hydrogen Reactions with Pd/C and ZnO: Diol Scope, *Tetrahedron Letters* (2017), doi: https://doi.org/10.1016/j.tetlet.2017.11.039

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Heterogeneous Borrowing Hydrogen Reactions with Pd/C and ZnO: Diol Scope

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Abstract

A borrowing hydrogen reaction with different diols was employed for the preparation of complex *beta- gamma-* or *epsilon-* amino alcohols from *p*-toluidine and tetrahydroquinoline with the aim of better understanding the applicability of the Pd/C ZnO heterogeneous catalyst.

Introduction

Borrowing hydrogen (BH) reactions,¹ also known as hydrogen auto-transfer (HA) reactions,² between amines and alcohols represent a unique opportunity to create molecular complexity from readily accessible reagents while being in coherence with green chemistry principals.³ Among the different methodologies proposed, Pd, Ru, Mn, Ir and Co complexes have shown significant relevance under homogeneous conditions.^{1b,4,5} Additionally, heterogeneous catalysts have been developed for this purpose.⁶ Diols represent challenging compounds in BH reactions, ethylene glycol for example has recently been employed, however, double reactions are common.^{4,7} In the course of our studies we have reported a catalyst combination (Pd/C 7 mol%, ZnO 3 equiv.)^{8a} which is able to mono activate ethylene glycol to create β-amino alcohols. Herein, we report an extension of this methodology to more complex alcohols in order to understand the limitations of this system (Scheme

1).



Scheme 1: BH/HA reactions with different diols

Results and Discussion

p-Toluidine **1a** and tetrahydroquinoline **1b** were selected as reagents using the same conditions that were employed for ethylene glycol **2**.^{8a} Indeed, in our previous studies these

compounds behaved differently under identical conditions; *p*-toluidine **1a** gave amino alcohol **3a** in excellent yields, and tetrahydroquinoline **1b** afforded a mixture of amino alcohol **3b** and indole **4** (Scheme 2).⁸ At this point, is important to note that β -amino alcohols are BH/HA products, however, indoles do not require the final hydrogenation steep. This is known as an acceptor-less dehydrogenate condensation (ADC)⁹ pathway which has been proposed as a powerful strategy for the preparation of heterocycles, and has been exclusively observed with **1b** under our conditions, but not with **1a**.



Scheme 2: Chemical behavior of *p*-toluidine 1a and tetrahydroquinoline 1b with ethylene glycol. NMR yields; isolated yields are given in parenthesis.

Propane 1,2-diol **5** was first selected due to its unsymmetrical structure (Scheme 3). When this diol was submitted to the reaction with *p*-toluidine **1a**, amino alcohol **6a** was formed in 95% yield (NMR); however, isolation from the remaining diol was difficult and resulted in only a 45% isolated yield. When tetrahydroquinoline **1b** was submitted to these conditions the corresponding amino alcohol **6b** was obtained in 30% yield (NMR), in the presence of a mixture of indoles **7** (85:15) which were obtained *via* an ADC process as previously reported.



Scheme 3: Chemical behavior of 1a and 1b with propane 1,2-diol 4. Isolated yields are given in parenthesis.

Although these results clearly reveal the selectivity of the process to afford α -substituted- β amino alcohols such as compounds **6a** and **6b**, it is important to note that the oxidation of asymmetrical diol **5** has been proposed to be affordable in both primary and secondary alcohols (Fig. 1; top).¹⁰ Oxidation on the primary alcohol affords aldehyde **8a** while oxidation of the secondary alcohol affords ketone **8b**. In addition a tautomeric equilibrium is present in this system through compound **8c**.¹¹ However, the more stable iminium intermediate (less steric hindrance) may be associated with the aldehyde alcohol **8a**. The lower yield for tetrahydroquinoline **1b** may also be related to steric hindrance. Being a cyclic amine **1b**, the iminium intermediate (Fig. 1, center) may possess steric hindrance due to the absence of free rotation. Both BH products (**6a** and **6b**) clearly indicate that the reaction of aldehyde **8a** is preferred. The corresponding ADC products **7** observed with tetrahydroquinoline **1b** also indicate this feature although a minimal 15% of the other isomer was present; this adds evidence for an equilibrium process.



Figure 1: Imine equilibrium during the formation of alcohol 5a.

When symmetrical propane diol **9** was submitted to the reaction conditions a mixture of products was also obtained (Scheme 4). For compound **1a**, 90% conversion was observed, however the corresponding BH product λ -amino acid **10a** was only obtained in 10% isolated yield. A major component of this reaction was the corresponding propyl amine **11a**. Dehydroxylation of these compounds is rare,¹² however Bruneau and co-workers previously observed this feature under homogeneous BH conditions, presumably involving elimination and hydrogenation reactions.¹³ Additionally, quinoline **12** was isolated in 15% yield, presumably *via* a Skraup-like mechanism.¹⁴



Scheme 4: Chemical behavior of *p*-toluidine and tetrahydroquinoline with propane 1,3-diol. Isolated yields are given in parenthesis.

Comparing these results with tetrahydroquinoline **1b**, similar behavior was observed, however the conversion was decreased. Compounds **10b** and **11b** were obtained in poor yields. Under these conditions quinolines were not observed since secondary amines such as tetrahydroquinoline cannot afford these kinds of products.

Finally, diol 13 was employed with the aim of exploring more complex systems. Diol 13 contains a central ether that in principle should avoid any tautomeric pathways, thus, only ε -amino alcohols should be expected. Indeed *p*-toluidine 1a afforded compound 14a in good yield (Scheme 5), however isolation from the remaining diols proved difficult (38% isolated yield). Nevertheless, this methodology did not require desymmetrization of diol 13. Similar results were obtained with 1b, albeit in lower yield; in this case no side-products were observed.



Scheme 5: Chemical behavior of *p*-toluidine 1a and tetrahydroquinoline 1b with diethylene glycol 12. Isolated yields are given in parenthesis.

Conclusion

The combination of Pd/C and ZnO has been proven to be an adequate heterogeneous catalyst for the single-alcohol activation of different diols, with particularly interesting results

obtained using propane-1,2-diol **5** and diethylene glycol **13**. In all cases the corresponding amino alcohols could be obtained, thus this methodology represents a different approach for the preparation of these compounds. No derivatization of the diols was required and all reactions were performed in water:diol mixtures. The use of 1,3-propanodiol **9** afforded dehydroxylated compounds **11a** and **11b** and quinoline **12** *via* a Skraup-like mechanism.

Associated Content

Supporting Information.

Experimental procedure, compound characterization and ¹H- and ¹³C-NMR spectra of new compounds (PDF).

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Notes

The authors declare no competing financial interest.

Acknowledgements

R. B-G is much indebted to the Postdoctoral fellow 2013 of the "Ministerio de Economía y Competitividad" (Spain, FPDI-2013-17464). This work was financially supported by the "Ministerio de Ciencia e Innovación" (Spain) (Project CONSOLIDER-INGENIO SUPRAMED CSD 2010-00065 and from University of Valencia (Spain) (UV-INV-AE 15-332846)). Acknowledgments to the "Central Services for Experimental Research" (SCSIE) of University of Valencia and NANBIOSIS platform. We gratefully acknowledge the suggestions and advice from the referee and the editor in order to improve the quality of this contribution.

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Mono functionalization of diols is achieved with heterogeneous borrowing hydrogen catalyst.

Evidences of tautomeric equilibrium are found.

Diethylene glycol can be used to prepare epsilon amino alcohols with central ether.

Pd/C, ZnO Combination can be applied to other diols different from ethylene glycol.



