#### Letter

# Effective Conversion of Heteroaromatic Ketones into Primary Amines via Hydrogenation of Intermediate Ketoximes

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Received: 29.09.2014 Accepted: 20.10.2014 Published online: 02.12.2014 DOI: 10.1055/s-0034-1379538; Art ID: st-2014-r0821-l

**Abstract** A process to access heteroaromatic primary amines from the corresponding heteroaromatic ketones has been developed. A broad range of previously reported methods to convert ketones to primary amines was examined on heterocyclic ketones without success, including Leuckart–Wallach conditions, borane reductions, and transition-metal-catalyzed hydrogenations. Unique among the catalysts examined, Raney cobalt produced the desired primary heterocyclic ketoximes was demonstrated to form primary amines in good selectivity under mild conditions, and the products are easily isolated in high yield. Additionally, this is the first report of a systematic evaluation of the capabilities of Raney cobalt as an oxime hydrogenation catalyst.

Key words hydrogenation, Raney cobalt, heterogeneous catalysis, amines, reduction, heterocycles

The conversion of ketones to the corresponding primary amine is a common and useful transformation in organic synthesis. This transformation is typically achieved by reductive amination via reduction of an imine or enamine derived from the corresponding ketone.<sup>1</sup> Alternately, the reduction of oximes and nitriles can lead to the same products, typically requiring stoichiometric reductants such as Mg, Na, Zn, Fe plus a hydride source or borane reagents. These procedures can be expensive, pose environmental concerns and involve complicated workup procedures.<sup>2</sup> Solid-supported metals like Pd, Ni or Rh can be used as hydrogenation catalysts, avoiding expensive stoichiometric reagents and complex isolation protocols.<sup>3</sup> However, oxime reductions using these systems can be incompatible with heteroaromatic functionalities due to complexation of the metal catalyst by the heteroatom-containing substrates and halogen-containing substrates due to dehalogenation.

As part of a program to develop an improved synthesis towards an advanced intermediate of a kinase inhibitor, we sought to transform a heteroaromatic ketone into the corresponding primary amine (Scheme 1). Conventional direct amination methods were explored with little success. Leuckart–Wallach conditions led to significant decomposi-



tion and only produced trace amounts of the desired amine.<sup>4</sup> Other reductive amination conditions investigated produced the primary amine in poor to modest yields (40–60%) with the remainder of the mass balance forming the secondary amine (formed from two equivalents of the parent ketone) or alcohol.<sup>5</sup>



**Scheme 1** Synthesis of an amine from a ketone containing a coordinating heterocycle and associated reaction side products

Encouraged by reports from Shan where oxime ethers were readily reduced in the presence of stoichiometric borane reagents, we pursued amine formation through oxime reduction.<sup>6</sup> A model chelating heteroaromatic ketone **1** was converted into a ketoxime **2** to examine the feasibility of this approach (Scheme 2).



Scheme 2 Model oxime synthesis for reduction studies

A variety of borane reagents failed to reduce **2** to the desired amine **3**. Instead, the starting oxime was recovered unchanged; prolonged reaction times led to complex degradation. Zinc- and magnesium-mediated reductions gave

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poor conversions to the desired amine even after extended reaction times and forcing conditions.<sup>2a,e</sup> We then turned our attention to hydrogenation of the oxime moiety.<sup>7</sup> After screening a variety of heterogeneous catalysts (Table 1), we found that palladium and platinum gave no desired amine. Pd- and Pt-catalyzed the reduction of the C–N double bond yielding the hydroxy amine derived from **2**. Ruthenium and rhodium gave only low conversion (<5%), presumably due to chelation-induced deactivation of the metal catalyst by the bipyridyl functionality of the substrate. Raney nickel showed consumption of the oxime **2**, but produced a complex mixture of products with little to no desired amine observed.

However, Raney cobalt 2724 reduced oxime **2** to primary amine **3** in >95% yield and excellent purity, suppressing the secondary amine formation to <1% (Table 1, entry 6). The amine product could easily be isolated from this reaction by filtering off the heterogeneous catalyst then adding HCl to precipitate the product as a salt. This reaction was subsequently demonstrated on >10 gram scale.

A few isolated reports of oxime reduction by Raney cobalt were present in the literature.<sup>8</sup> However, to the best of the authors' knowledge, this report represents the first systematic study of a high-yielding oxime reduction by this underutilized heterogeneous catalyst.

The scope of the Raney cobalt 2724 catalyst was then examined using the process developed for the model substrate (Table 2). Sterically encumbered oximes were well tolerated (Table 2, entries 2–6). Substrates expected to strongly coordinate cobalt did not interfere with the reaction (Table 2, entries 1 and 7), and aromatic halide-containing oximes could be reduced without significant dehalogeTable 1Examination of Heterogeneous Catalysts in the Reduction ofOxime 2



<sup>a</sup> Raney catalysts are stored and charged as a slurry in  $H_2O$ . The slurry was charged at 100 wt% relative to oxime. <sup>b</sup> Purchared from W. P. Crace and Co.

<sup>b</sup> Purchased from W. R. Grace and Co.

nation (Table 2, entries 10 and 11). Competitive secondary amine formation was an issue for less sterically congested substrates (Table 2, entries 2, 8, 12, and 13 and Scheme 3). In particular, aldoximes preferentially formed dimeric secondary amines and yielded very little primary amine product (Table 2, entries 12 and 13). The formation of secondary amines during oxime and nitrile formation has been previously observed and reported. Specifically, Müller has observed that the choice of catalyst can influence the selectivity of amine formation.<sup>8b</sup>



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### Table 2 (continued)

Entry	Starting material	Product	Yield
4	NOH CH <sub>3</sub> 2d	$H_2$ $H_3$ $H_3$ $H_3$	86%
5	NOH CH <sub>3</sub> CH <sub>3</sub> 2e	$H_2$ $CH_3$ $CH_3$ $CH_3$ $CH_3$	98%
6	NOH 2f	NH <sub>2</sub> 3f	95%
7	NOH 2g	NH <sub>2</sub> 3g	90%
8	NOH CH <sub>3</sub> 2h	$H_2$ CH <sub>3</sub> Sh	25%ª
9	H <sub>3</sub> C NOH CH <sub>3</sub> 2i	H <sub>3</sub> C N CH <sub>3</sub>	85%
10	CI NOH 2j		80%
11	CI NOH	CI NH2 3k	88%
12	NOH N 21	NH <sub>2</sub> 3I	<10% <sup>a</sup>
13	2m NoH	3m	40%ª

<sup>a</sup> A 100% conversion of starting material was observed. Mass balance was conversion to the corresponding dimeric secondary amine (Scheme 3).

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**Svnlett** K. D. Baucom et al.  $NH_2$ NOH Raney Co THF-MeOH 21 31 4 H<sub>2</sub> (60 psi) 50 °C, 12 h 90% <10% assay yield assay yield Scheme 3 Ranev cobalt reduction of aldoximes

Direct reduction of nitriles with this catalyst system was also examined. Subjecting nitriles to the reaction conditions developed herein leads to the formation of dimeric amines as the major reaction products (Scheme 4). This presumably occurs via similar mechanism and intermediates as the previously reported results from the reduction of aldoximes.



In summary, we have developed a convenient procedure to access heterocyclic primary amines via hydrogenation of the corresponding oxime using Raney cobalt 2724 as the catalyst.<sup>9</sup> This is the first such study of amine synthesis from oximes utilizing this catalyst. The reaction conditions are mild and can tolerate the presence of reductively labile halogen functionality and strongly coordinating heterocycles. Furthermore, the products are readily separated from the catalyst by simple filtration and can be purified by chromatography or salt formation.

## Acknowledgment

We thank Dr. Matthew M. Bio and Dr. Shawn D. Walker (Amgen) for their review of the manuscript and helpful discussions.

## **Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379538.

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- (9) **General Oxime Procedure**: Ketone (76 mmol), hydroxylamine hydrochloride (83 mmol), NaOAc (83 mmol) and EtOH (140 mL) were combined and heated to reflux for 3 h. White solid (oxime) was observed to precipitate from the solution during this time. The mixture was then cooled, deionized  $H_2O$  (140 mL) was added, and the mixture was then stirred for 10 min. The solids were isolated by filtration, washed with  $H_2O$  (140 mL) and dried at r.t. under nitrogen flow on the filter.

**General Reduction Procedure**: To a mixture of oxime (0.86 mmol) and Raney Co 2724 (200 mg, slurry in  $H_2O$ ) were added THF (1.5 mL) and MeOH (1.5 mL). The reaction mixture was purged with nitrogen twice then pressurized to 60 psi  $H_2$  at 50 °C. The reaction was deemed complete when  $H_2$  consumption ceased, typically after 2–10 h. Upon completion, the reaction was filtered through a pad of celite and washed with MeOH. The filtrate was then concentrated under reduced pressure, and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>–MeOH, 95:5) to furnish the title compound. Alternatively, the product was conveniently isolated in high purity as the HCl salt. After filtering off the catalyst, the filtrate solvent was changed to MTBE (1.5 mL) and HCl (0.95 mmol, 1 M in Et<sub>2</sub>O) was added dropwise to crystallize the salt. The resulting HCl amine salt was then isolated by filtration and washed with MTBE.

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