Journal Name

COMMUNICATION

Hydroamination of alkenyl *N*-arylhydrazones mediated by *t*-BuOK for synthesis of nitrogen heterocycles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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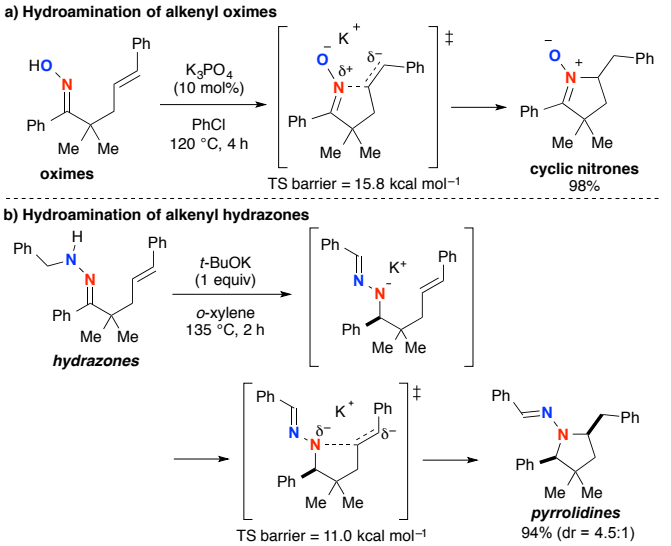
***t*-BuOK–mediated reactions of γ,δ-alkenyl *N*-arylhydrazones enabled intramolecular hydroamination with the outer nitrogen, affording tetrahydropyridazine derivatives. DFT calculations demonstrated a clear distinction in chemical reactivity between hydrazones and analogous oximes in inorganic base-mediated hydroamination.**

As one of the most efficient ways to construct nitrogen-heterocycles,[1,2] intramolecular hydroamination of alkenyl amines and their derivatives have been intensively studied with various metal complexes (alkali metals, transition metals, and f-block elements) as well as Brønsted acids.[3,4] We have recently studied inorganic base-mediated hydroamination of alkenyl oximes and hydrazones for the synthesis of nitrogen-heterocycles.[5] The reactions of γ,δ-alkenyl oximes mediated by potassium bases such as K_3PO_4 and *t*-BuOK proceeded in a unprecedented fashion to yield 5-membered ring nitrones, which were formed via nucleophilic amination of unactivated alkene by the oxime nitrogen (Scheme 1-a).[5a] Density functional theory (DFT) calculations suggested that the ionic interaction between the potassium cation on the oxime oxygen and the negatively charged alkene moiety stabilizes the transition state. On the other hand, *t*-BuOK-mediated reactions of γ,δ-unsaturated *N*-alkylhydrazones led to the construction of pyrrolidine skeletons via hydrazone-hydrazone isomerization with 1,3-proton shift followed by the nucleophilic hydroamination; in this reaction, modification of the substituents on the hydrazone moiety greatly affected the diastereoselectivity (Scheme 1-b).[5b] Based on these findings, we wondered whether γ,δ-alkenyl *N*-arylhydrazones, for which hydrazone-hydrazone isomerization is not possible, undergo cyclization in the same way as the oximes, to form the corresponding 5-membered ring azomethineimines or afford tetrahydropyridazines via 6-exocyclization with the outer nitrogen.[6,7] We herein report the results from our experimental and theoretical studies to address this question.



Scheme 1 Inorganic Base-Mediated Hydroamination of Alkenyl Oximes and Hydrazones

Our investigation was commenced with the reactions of γ,δ-alkenyl *N*-phenylhydrazone **1a** (Table 1). The reaction with 1 equiv of *t*-BuOK[8] in *o*-xylene proceeded at 135 °C (entry 1), resulting in formation of 6-membered ring tetrahydropyridazine **2a** in 62% yield via hydroamination of alkene with the outer nitrogen atom (marked in blue), while formation of azomethineimine **2a'** was not observed at all. Further optimization of the reaction conditions revealed that addition of Et_3COH as an additive could improve the yield of **2a** (entry 2). The reactions with catalytic amounts of *t*-BuOK were not optimal for this reaction (entries 3 and 4). The reaction in DMF performed well (entry 5), while that in DMSO became sluggish (entry 6). It is noted that the reactions of **1a** with *t*-

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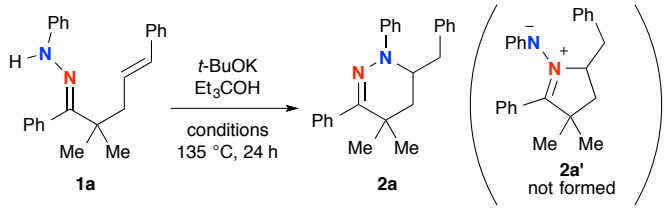
Electronic Supplementary Information (ESI) available: Electronic Supplementary Information (ESI) available: Experimental details, including procedures, syntheses and characterization of new compounds; ^1H and ^{13}C NMR spectra. CCDC 1436809 – 1436815. See DOI: 10.1039/x0xx00000x

BuOLi and *t*-BuONa as well as other potassium bases such as K_3PO_4 and K_2CO_3 gave no hydroamination product **2a**.

Table 1 Optimization of reaction conditions[a,b]



Entry	*t*-BuOK (equiv)	Et_3COH (equiv)	Solvent	Yield of **2a** (%)[b]
1	1	0	*o*-xylene	62 (23)[c]
2	1	3	*o*-xylene	84
3	0.2	3	*o*-xylene	10 (82)[c]
4	0.4	3	*o*-xylene	44 (50)[c]
5	1	3	DMF	62(11)[c]
6	1	3	DMSO	42

[a] Unless otherwise noted, the reactions were carried out in the scale of 0.5 mmol of hydrazone **1a** in solvent (5 mL) under an Ar atmosphere. [b] Isolated yields were recorded. [c] Recovery yields of **1a** based on ^{1}H NMR.

Having observed the distinct reaction outcomes for inorganic-base mediated hydroamination of oximes (Scheme 1-a) and *N*-phenylhydrazone **1a**, we performed DFT calculations at the B3LYP/6-311+G(d,p) level using Gaussian 09,[9-11] to gain mechanistic insights. We examined 5-membered (Path A) and 6-membered ring formation (Path B) pathways. The solvent effect of *o*-xylene was included in the calculation using the IEFPCM method,[12] and frequency calculation was performed for each optimized geometry, which yielded a zero-point vibrational energy (ZPE) value. Figure 1a shows the energy profile obtained for the reaction of hydrazone **1a**.[13] Sequence of deprotonation and protonation allows facile E/Z isomerization of the N-N bond through diazene intermediate 1a'. The relative energy of the transition state for for the 6-membered ring formation (**TS1a-A-E**) is not too high (20.2 kcal mol^{-1}) with respect to **1a-A-Z**, consistent with the experimental fact that the reaction of hydrazone **1a** yielded **2a**. Nevertheless, organopotassium intermediate **2a-A** is higher in energy than the reactant state (**1a-A-Z**) by 19.1 kcal mol^{-1}, which will render the equilibrium between these two states largely in favor of the reactant state. The reason why the yield of **2a** became higher in the presence of Et_3COH is probably because Et_3COH donates a proton to carbanion **2a-A** to facilitate the reaction in the forward direction.[14]

The DFT calculations further showed that the reaction of hydrazone **1a** favors 6-membered ring formation (path B) over 5-membered ring one (path A). In fact, a local energy minimum corresponding to a 5-membered ring intermediate did not exist on the potential energy surface (see Figure 1b, path A). This trend is markedly different from that for the oxime substrate, which favors 5-membered ring formation (Figure S1).[5a] In contrast to the case of hydrazone, a 6-membered ring intermediate was not obtained for the oxime substrate (Figure S3). To identify the reason that hydrazone **1a** selectively undergoes 6-membered ring formation, we inspected the highest occupied molecular orbitals (HOMOs). The HOMO of **1a-A-E** is a π-type orbital, which extends perpendicularly to the C=N–N plane, while the HOMO-1 is an in-plane lone-pair type orbital (Figure 2a). The latter orbital will be mainly responsible for the nucleophilic attack on the alkene carbon. The HOMO-1 has large distributions on both of the two nitrogen atoms of the hydrazone moiety, suggesting that these two nitrogen atoms are almost equally reactive. However, 5-membered ring formation causes a significant steric clash between the phenyl groups on the hydrazone and alkenyl moieties. To prevent this steric clash, the C=N–N–Ph moiety undergoes rotation, which disrupts the stabilization gained by conjugation (Figure 2b, path A). The C–N–N–C tortion angle of this moiety was -138.2° at r = 1.8 Å, indicating significant loss of planarity. By contrast, the steric clash is much less severe in the 6-membered ring formation, as reflected by the almost unaltered planarity of this moiety at **TS1a-A-E** (tortion angle = 175.4°, see Figure 2b, path B). These explain why a 6-membered ring is preferentially formed in the hydroamination of hydrazone **1a**.[15]

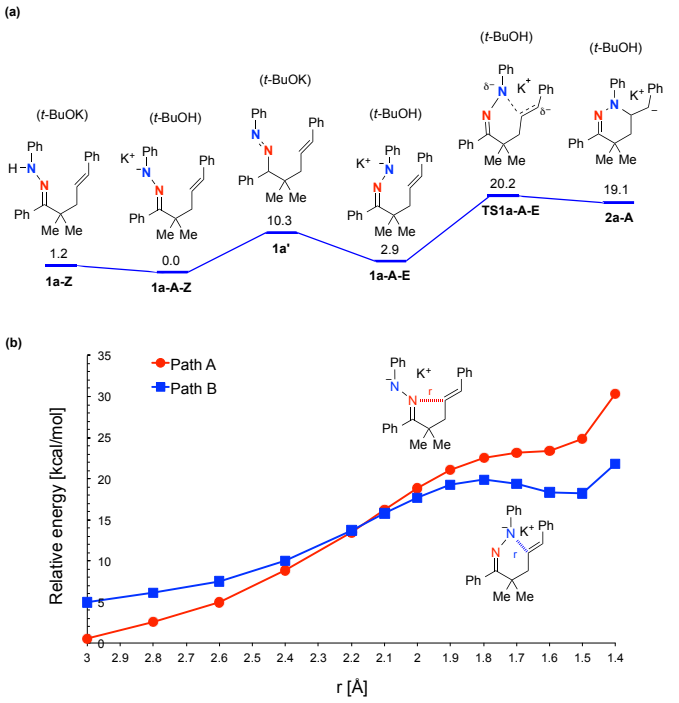


Figure 1 (a) Energy diagrams (in kcal mol^{-1}) for the reaction of deprotonated hydrazone, determined at the B3LYP(IEFPCM)/6-311+G(d,p) level with ZPE corrections. (b) Variation of energy (in kcal mol^{-1}) with decreasing N–C bond distance, as obtained from relaxed energy calculations.

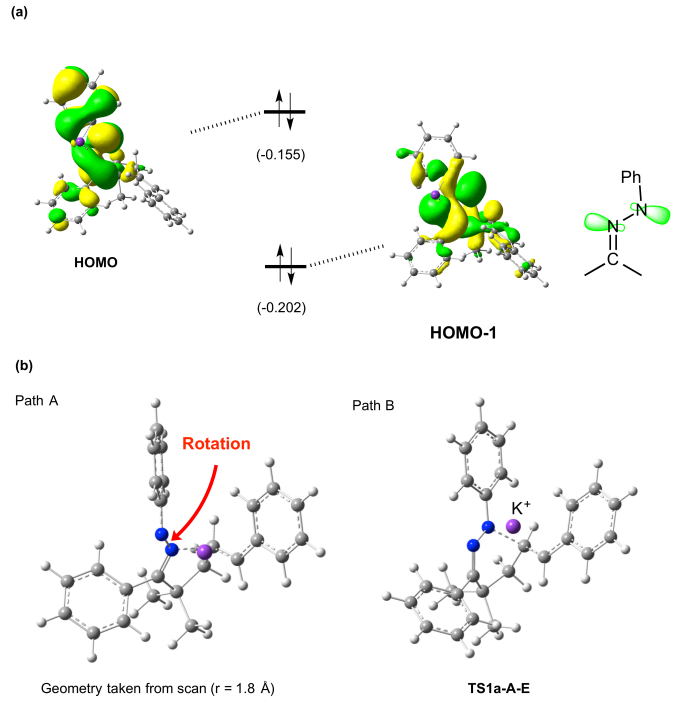
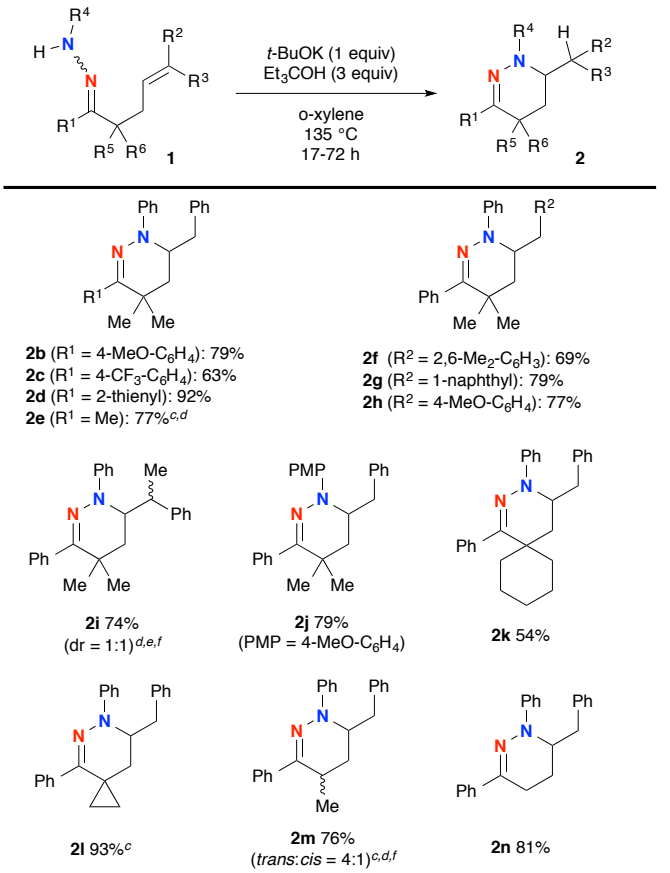


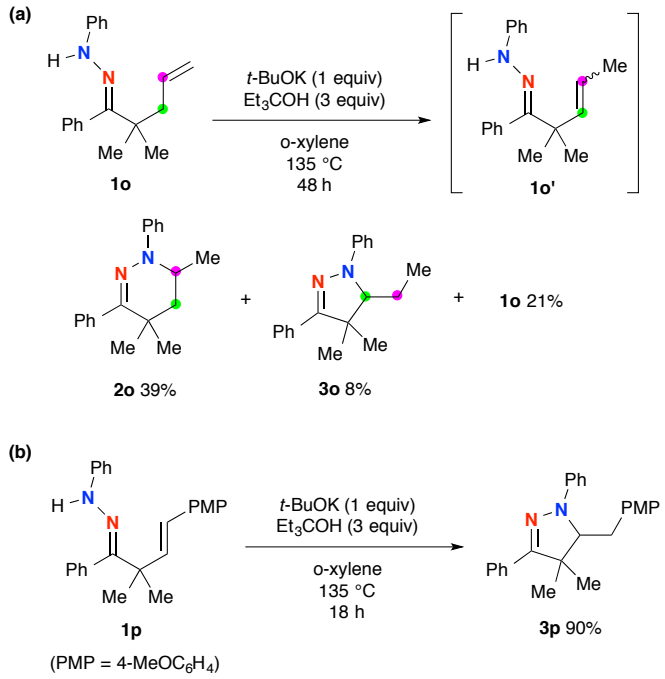
Figure 2 (a) HOMO and HOMO-1 of **1a-A-E**. The values in parentheses are orbital energy levels in hartrees. (b) Geometries of **1a-A-Z** at r = 1.8 Å (left) and **TS1a-A-E** (right).



Scheme 2 [a] Unless otherwise noted, the reactions were carried out in the scale of 0.5 mmol of hydrazones **1** in o-xylene (5 mL) under an Ar atmosphere. [b] Isolated yields were recorded. [c] The 2-step yield from ketone (0.5 mmol) via hydrazone formation and hydroamination was noted. See the Supporting Information for more details. [d] The reaction was conducted in the presence of *t*-BuOH (10 equiv) instead of Et_3COH. [e] The reaction was conducted using 0.3 mmol of **2i**. [f] The diastereomeric ratio was judged by ^1H NMR analysis of the isolated mixture of **2** and shown in parentheses.

Having obtained the optimal reaction conditions for hydroamination of hydrazone **1a** (Table 1, entry 2) and an understanding of the reaction mechanism, we next examined the substrate scope using a variety of hydrazones **1** (Scheme 2). Reactions with varying R^1 allowed for the installation of not only aryl/heteroaryl units (for **2b-d**) but also a methyl group (for **2e**), while maintaining good product yields. We then turned our attention to the substituents on the alkene (R^2 and R^3). Steric effects did not influence the reaction outcome for hydroamination of aryl alkenes (for **2f** and **2g**). Hydroamination with even an electron-rich aryl alkene (for **2h**) proceeded smoothly. The reaction of hydrazone **1i** having the trisubstituted *E*-alkene with Ph as R^2 and Me as R^3 did not retain alkene stereochemistry in the present hydroamination step, affording a 1:1 diastereomeric mixture of **2i**. This result implies that the present hydroamination proceeds in a stepwise manner via the carbanion intermediate like **2a-A** in Figure 1. The reaction of *N*-(para-methoxyphenyl)hydrazone **1j** gave a good yield of hydroamination product **2j**. Spirocyclic structures could be constructed in moderate to good yields (for **2k** and **2l**). The reactions of **1m** and **1n** having α-proton(s) proceeded well to give the corresponding tetrahydropyridazines **2m** and **2n** in 76% and 81% yields, respectively.

The present hydroamination of hydrazones was applied to the functionalization of terminal alkene **1o**, which gave tetrahydropyridazine **2o** and dihydropyrazole **3o** in 39% and 8% yields, respectively, along with 21% recovery of **1o** (Scheme 3-a). Dihydropyrazole **3o** was formed presumably via 5-exo cyclization of β,γ-unsaturated hydrazone **1o'**, which is generated via alkene isomerization from terminal to internal under the present reaction conditions. Indeed, the present hydroamination method enabled us to construct dihydropyrazole **3p** in 90% yield via 5-exo hydroaminative cyclization of β,γ-unsaturated hydrazone **1p** (Scheme 3-b).



Scheme 3 [a] The reactions were carried out in the scale of 0.5 mmol of hydrazones **1** in o-xylene (5 mL) under an Ar atmosphere. [b] Isolated yields were recorded above.

In summary, we have developed *t*-BuOK-mediated hydroamination of alkenyl N-arylhydrazones mainly for the synthesis of tetrahydropyridazine derivatives. Hydrazones have exhibited a wide spectrum of chemical reactivity owing to their unique chemical structure.[16] In the area of azaheterocycle synthesis, hydrazones have been typically utilized in the Fischer indole synthesis[17] and as a precursor of azomethine imine 1,3-dipoles for [3+2]-cycloaddition with dipolarophiles.[18,19] The present work offers a new reaction entry of hydrazones towards azaheterocycle synthesis, which is enabled by a simple operation with *t*-BuOK.

This work was supported by funding from Nanyang Technological University (NTU) and the Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2012-T2-1-014). H.H. thanks the High Performance Computing Centre of NTU for computer resources.

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15 On the other hand, the HOMO of the deprotonated oxime is an in-plane orbital (see the Supporting Information, Figure S4). The HOMO lobe is highly localized on the nitrogen, especially on the side of new bond formation, which is beneficial for 5-membered ring formation. However, the HOMO lobe on the oxygen atom looks like a pure p-orbital and is nearly perpendicular to the N–O bond. Thus, the oxygen may not be able to interact with the alkene effectively (Figure S5b). These characteristics of the HOMO seem to provide a rationale for the observation that formation of a 5-membered ring is preferred in the oxime case.

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