J|A|C|S COMMUNICATIONS

Published on Web 06/08/2009

Hydrazides as Tunable Reagents for Alkene Hydroamination and Aminocarbonylation

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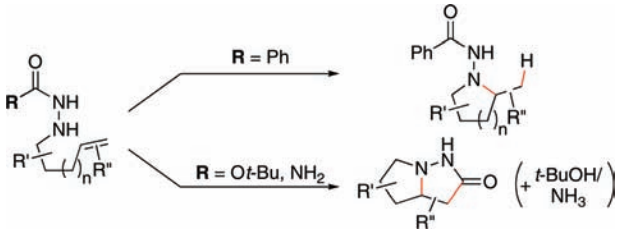
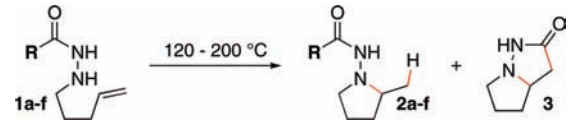
Since over 90% of pharmaceuticals have at least one nitrogen atom in their structure and as approximately one reaction out of six performed in the pharmaceutical industry involves the formation of a carbon−nitrogen bond, the development of efficient routes to nitrogen-containing molecules is of paramount importance.[1] Amination reactions involving electron-rich alkenes offer excellent potential for broad applicability, which continues to attract intense research interest. Various methodologies have been developed, and transition metal catalysts are typically used to *enable* amination reactivity. In efforts directed toward metal-free hydroamination,[2,3] we recently extended the scope of Cope-type hydroaminations of hydroxylamines to intermolecular reactions of alkenes, alkynes, and allenes.[4,5] Given that hydroxylamines can be sensitive and prone to decomposition, more practical reagents were sought to extend the reaction scope. Herein we report that benzoic hydrazides (**R** = Ph), which are remarkably bench and thermally stable (often up to 230 °C), offer a practical alternative to perform Cope-type hydroaminations.[6,7] In addition, a simple modification of the reagent structure (**R** = O*t*-Bu, NH_2) leads to alkene aminocarbonylation products under metal-free conditions.[8]



A simple system yielding a pyrrolidine ring upon cyclization was first investigated to validate the hydroamination (HA) reactivity. Gratifyingly, the desired product **2a** was formed upon heating phenyl hydrazide **1a** at 120 °C (Table 1, entry 1). The parent pyridyl and *tert*-butyl hydrazides also formed the HA product, albeit at higher temperatures (entries 2−3). Fortuitously, oxygen-substituted reagents yielded a mixture of HA and aminocarbonylation products under similar conditions (entries 4−5). Further studies showed that aminocarbonylation is favored at higher temperatures (entry 6) and that nitrogen analogues also display similar reactivity (entries 7−8). A preliminary substrate scope for intramolecular hydroamination and aminocarbonylation reactivity of hydrazides is presented in Tables 2 and 3, respectively.

As shown in Table 2, various benzoic hydrazides cyclize efficiently to form intramolecular hydroamination products. Five- and six-membered azacycles are formed reliably (entries 1−11). Both primary and secondary hydrazides react under similar reaction conditions (entries 1 and 2), and heteroatoms can be present in the substrate as illustrated by the formation of a morpholine (entry 7)

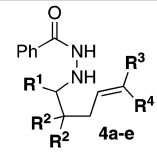
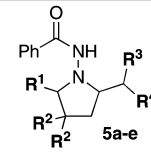
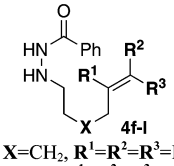
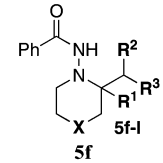
Table 1. Optimization of Hydroamination/Aminocarbonylation Reactivity[a]



entry	conditions[a]	R	product(s) and yield(s)[b]
1	120 °C, 18 h	Ph	**2a** (93%)
2	150 °C, 16 h	*t*-Bu	**2b** (66%)
3	170 °C, 42 h	2-pyridyl	**2c** (64%)
4	140 °C, 16 h	OEt	**2d** (25%)[c] + **3** (6%)
5	200 °C (μw), 5 h	OEt	**2d** (13%) + **3** (46%)
6	200 °C (μw), 5 h	O*t*-Bu	**2e** (0%) + **3** (71%)
7	150 °C (μw), 5 h	NH_2	**2f** (50%) + **3** (20%)[d]
8	200 °C (μw), 15 min	NH_2	**2f** (10%) + **3** (85%)[d]

[a] Heating performed in $PhCF_3$ (0.05 M, sealed tube) unless indicated otherwise. [b] Isolated yield. [c] Other hydroamination byproducts are formed [Σ_{HA} products = 76% (^{1}H NMR)]. [d] NMR yield using an internal standard.

Table 2. Scope of Intramolecular Hydrohydrazidation Reactivity[a]

entry	alkenyl hydrazide	temp (°C)	product	yield[b] %
	 4a-e		 5a-e	
1	**R**^{1}=**R**^{2}=**R**^{3}=**R**^{4}=H	120	**5a**	93
2	**R**^{1}=Me, **R**^{2}=**R**^{3}=**R**^{4}=H	120	**5b**	98[c]
3	**R**^{1}=**R**^{2}=H, **R**^{3}=Me, **R**^{4}=H	175	**5c**	61
4	**R**^{1}=**R**^{2}= **R**^{3}=H, **R**^{4}=Me	175	**5d**	75
5	**R**^{1}=H, **R**^{2}=Me, **R**^{3}=**R**^{4}=H	85	**5e**	96
	 4f-l		 5f-l	
6	**X**=CH_2, **R**^{1}=**R**^{2}=**R**^{3}=H	200	**5f**	90
7	**X**=O, **R**^{1}=**R**^{2}=**R**^{3}=H	200	**5g**	75
8	**X**=NTs, **R**^{1}=**R**^{2}=**R**^{3}=H	200	**5h**	81
9	**X**=NTs, **R**^{1}=Me, **R**^{2}=**R**^{3}=H	200	**5i**	84
10	**X**=CH_2, **R**^{1}=**R**^{3}=H, **R**^{2}=Et	220	**5j**	51[d]
11	**X**=CH_2, **R**^{1}=**R**^{2}= H,**R**^{3}=Et	220	**5k**	47[d]
12	**X**=$(CH_2)_2$, **R**^{1}=**R**^{2}=**R**^{3}= H	235	**5l**	39[d]

[a] Heating performed in $PhCF_3$ (0.05 M), in sealed tubes (1−5) or μw (6−12). [b] Isolated yield. [c] 2.4:1 dr. [d] NMR yield using an internal standard.

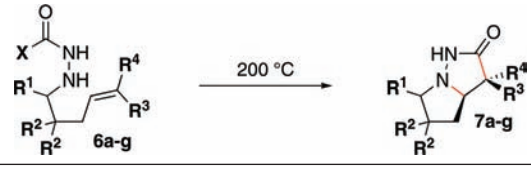
and two piperazines (entries 8 and 9). Several alkene substitution patterns are also tolerated, although higher reaction temperatures are required (entries 2, 3, 10, and 11). The reactivity shown in

10.1021/ja902558j CCC: $40.75

entries 10 and 11 is noteworthy since most reported examples of piperidine ring formation via hydroamination have been reported for terminal alkenes. Overall, this hydroamination procedure is experimentally simple and compatible with various solvents,[9] the cyclization precursors are typically bench-stable crystalline solids, and the products can be purified by chromatography.

DFT studies were performed to gain more insight into this hydroamination (HA) reactivity and support the pathway shown in eq 1. Calculated activation energies for a concerted, planar, five-membered Cope-type HA transition state ($\Delta G_{HA}^{\ddagger}$) were determined to be 28.7 and 34.2 kcal/mol for substrates **4a** and **4f**, respectively. For comparison, calculated values for the parent hydroxylamines are 22.9 and 27.2 kcal/mol. Our calculations also support the involvement of the carbonyl group of the hydrazide in the proton transfer step of the dipole intermediate formed by hydroamination ($\Delta G_{PT}^{\ddagger} = 5.2$ kcal/mol),[9,10] which is consistent with the reaction's compatibility with various solvents. The transition state structures for the hydroamination (**A**) and proton transfer (**B**) processes of substrate **4a** are shown in Figure 1. Overall, these results are in agreement with the higher temperatures required for the cyclization of hydrazides, which are typically 80−100 °C above that of the parent hydroxylamines.

Table 3. Scope of Intramolecular Aminocarbonylation Reactivity[a]



entry	alkenyl hydrazide	X	product	yield [b] %
1	$\mathbf{R^1}$=$\mathbf{R^2}$=$\mathbf{R^3}$=$\mathbf{R^4}$=H	O*t*-Bu	**7a**	70
2	”	NH_2	**7a**	86
3	$\mathbf{R^1}$=Me, $\mathbf{R^2}$=$\mathbf{R^3}$=$\mathbf{R^4}$=H	O*t*-Bu	**7c**	74[c]
4	”	NH_2	**7c**	84[c]
5	$\mathbf{R^1}$=$\mathbf{R^2}$=H, $\mathbf{R^3}$=Me, $\mathbf{R^4}$=H	O*t*-Bu	**7e**	66
6	”	NH_2	**7e**	52[d] (*+13%* **7g**)
7	$\mathbf{R^1}$=$\mathbf{R^2}$=$\mathbf{R^3}$=H, $\mathbf{R^4}$=Me	O*t*-Bu	**7g**	71

[a] Heating performed in MeCN (200 °C, 30 min, 0.05 M, microwave reactor). [b] Isolated yield. [c] 2:1 dr. [d] NMR yield using an internal standard.

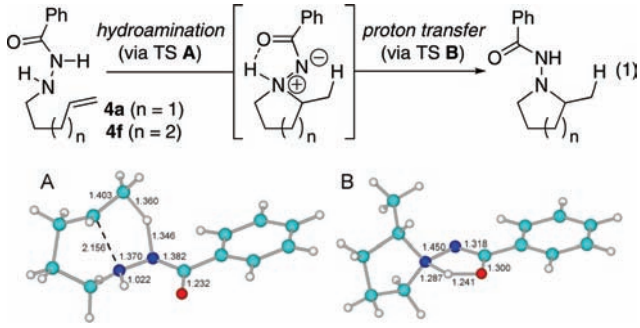


Figure 1. Transition state structures for the intramolecular hydrohydrazidation (**A**) and subsequent proton transfer of the dipolar intermediate (**B**) for substrate **4a**. The internuclear distances (Å) are shown only for relevant chemical bonds.

In contrast to benzoic hydrazides, carbazates (**X** = O*t*-Bu) and semicarbazides (**X** = NH_2) form aminocarbonylation products at elevated temperatures (Table 3). A preliminary substrate scope suggests that semicarbazides are superior precursors (entries 1−6). Both primary and secondary semicarbazides react under similar reaction conditions (entries 1−4). Alkene substitution at the distal position is also tolerated, and the reaction is a *stereospecific*[11] *syn addition* process (entries 5 and 6 vs 7). This reactivity appears consistent with in situ formation of an aminoisocyanate intermediate upon thermolysis above 150 °C,[12] followed by cycloaddition.[13]

In summary, we have shown that efficient intramolecular hydroamination and aminocarbonylation can be performed simply upon heating the appropriate hydrazine derivatives. Several extensions of this work are currently under investigation and will be reported in due course.

Acknowledgment. We thank the University of Ottawa, CFI, MRI (Ontario), NSERC, the Enantioselective Synthesis Grant (sponsored by the Canadian Society for Chemistry, AstraZeneca Canada, Boehringer Ingelheim (Canada) Ltd. and Merck Frosst Canada) for partial support of this work. We also thank Prof. Louis Barriault for an insightful discussion.

Supporting Information Available: Experimental procedures, solvent scan, computational details and spectroscopic characterization for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reaction can also be performed in PhMe, dioxane, MeCN, *i*-PrOH, DMF, and H_2O. See Supporting Information for details.

(10) For hydroxylamines, the proton transfer step of the N-oxide intermediate is kinetically relevant, and the increased reactivity observed in protic solvents (e.g., *n*-PrOH) is consistent with a bimolecular proton transfer process (e.g., *n*-PrOH-mediated). See refs 4a,b.

(11) Formation of product **7g** in entry 6 is consistent with epimerization of product **7e**. See Supporting Information for details.

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JA902558J