Improved Cope-type hydroamination reactivity of hydrazine derivatives†‡

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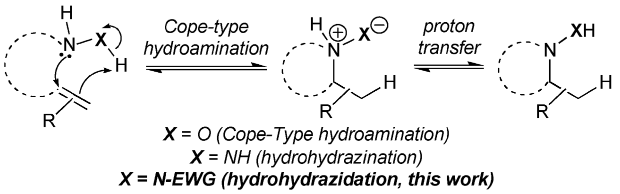
A systematic investigation on the metal-free, Cope-type hydroamination reactivity of hydrazides and analogues is reported. Optimization of the hydrazide structure resulted in more facile intramolecular reactivity and enabled intermolecular reactions of alkenes, thus providing a direct approach to polysubstituted hydrazides.

Efficient C–N bond-forming reactions continue to emerge from efforts to synthesize diverse nitrogen-containing functional groups from simple building blocks. Hydroamination, the formal addition of N–H bonds across an unsaturated carbon–carbon π bond, represents a highly desirable and versatile strategy to form C–N bonds. To overcome the high activation energy associated with such reactivity, hydroamination efforts have mostly focused on transition metal catalysis,[1] including some recent developments in hydrohydrazination.[2]

The availability of monosubstituted hydrazine derivatives has stimulated intense research and led to applications in agriculture (pesticides), polymer chemistry, photographic products and pharmaceuticals (both as synthetic intermediates and end products).[3] Specifically, hydrazides (*N*-acylhydrazines) have been used in the synthesis of heterocycles, dyestuffs, polymers, and in peptidomimetics (azapeptides),[4] agriculture (*e.g.* daminozide, a plant growth regulator) and pharmaceuticals [*e.g.* isoniacid (tuberculosis), isocarboxazid (antidepressant), atazanavir (antiretroviral)].[3c] With most applications featuring monosubstituted hydrazines and hydrazides, broadly applicable methods to access di- and tri-substituted hydrazines are in particular need. In this context, uses of hydrazines in the hydroamination of alkenes and alkynes (hydrohydrazination) are only emerging.[2]

As part of our interest in *metal-free* amination methods, we recently extended the scope of the thermal, concerted, Cope-type hydroamination[5] reactivity of hydroxylamines to intermolecular reactions of alkenes, alkynes and allenes (Scheme 1).[6] We also recently reported our preliminary results on related reactivity of hydrazines and hydrazides.[7] Herein, we disclose a systematic evaluation of the reactivity of hydrazine derivatives, leading to increased reactivity and applicability in intramolecular systems, and enabling intermolecular alkene hydrohydrazidation.



Scheme 1 Cope-type hydroamination of alkenes.

In contrast to hydroxylamines, hydrazine derivatives are remarkably thermally stable. Hydrazides are also typically crystalline and bench stable, and the electron-withdrawing group can facilitate the proton transfer step from the ammonium ylide intermediate.[6a,b,7] Speculating that optimizing the structure of the hydrazide group would result in a more facile hydroamination event (through stabilization of the developing charges present in the transition state) and stabilize the dipole intermediate, we embarked on a systematic investigation of related hydrazine derivatives (Table 1).

The data shown in Table 1 show the generality of the approach and allow a comparison of the relative reactivity of semicarbazides, thiosemicarbazides, phosphohydrazides and hydrazides in the formation of the pyrrolidine ring system (Table 1, entries 1–7). Due to side reactions observed with semicarbazides[8] and phosphohydrazides[9] at higher temperatures, benzoic hydrazides were selected for further optimization. Gratifyingly, increased reactivity was observed for substrates possessing hydrogen-bonding and electron-withdrawing substituents (entries 9–12). While both hydrazides **1j** and **1l** resulted in encouraging reactivity at 70 °C,[10] the increased solubility of hydrazide **1l** in organic solvents led us to explore the reactivity of 3,5-bis(trifluoromethyl)benzoic hydrazides in more challenging intra- and intermolecular reactions.

Thus, we next sought to investigate the cyclization of several substrates to access pyrrolidine and piperidine ring systems (Table 2). The reactivity of the simpler benzoic hydrazides[7a] (**4a–e**) is also presented to allow comparison.

As shown in Table 2, the efficiency of the cyclizations to simple 5- and 6-membered rings (**5a–e**) was comparable to that of the simple benzhydrazide derivatives (**6a–e**), with the hydroamination proceeding at lower temperatures. While only a modest increase in reactivity was observed, the effect of the improvement was most noticeable with substrates with distal alkene substituents (entries 5–6 and 9–10). Such disubstituted alkenes typically afford lower yields of the cyclised products due to a more challenging hydroamination event and competing side reactions.[11] In such systems, modified hydrazides resulted in a marked improvement over reactions obtained using benzoic hydrazides.

While intramolecular hydroamination reactivity is possible through various catalyzed and metal-free approaches,

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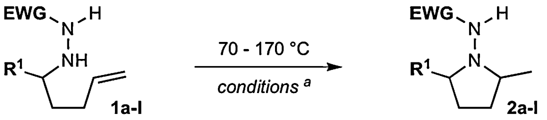
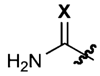
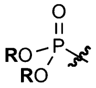
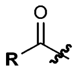
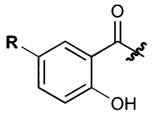
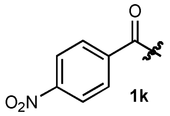
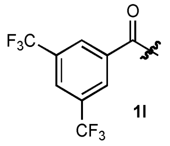
‡ Electronic supplementary information (ESI) available: Experimental procedures, optimization data for Table 3 and spectroscopic characterization for all new products. See DOI: 10.1039/c0cc02403a

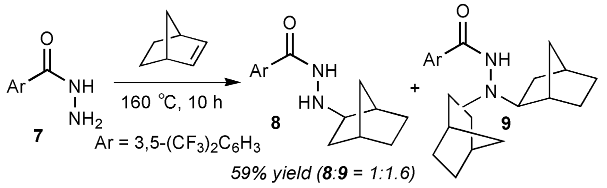
Table 1 Scope of intramolecular hydroamination using hydrazine derivatives



Entry	EWG	R^1	Temp/°C	Product	Yield[b] (%)
					
1	X = O (**1a**)	H	150	**2a**	50
2	X = S (**1b**)	H	100	**2b**	86
					
3	R = Et (**1c**)	H	120	**2c**	>98[c]
4	R = Ph (**1d**)	H	110	**2d**	>98[c]
					
5	R = *t*-Bu (**1e**)	H	150	**2e**	66
6	R = 2-pyridyl (**1f**)	H	170	**2f**	64
7	R = Ph (**1g**)	H	120	**2g**	93
8	R = Ph (**1h**)	Me	120	**2h**	98[d]
					
9	R = H (**1i**)	Me	90	**2i**	90[d]
10	R = NO_2 (**1j**)	Me	70	**2j**	88[d]
11	 **1k**	Me	90	**2k**	91[d]
12	 **1l**	H	95	**2l**	81

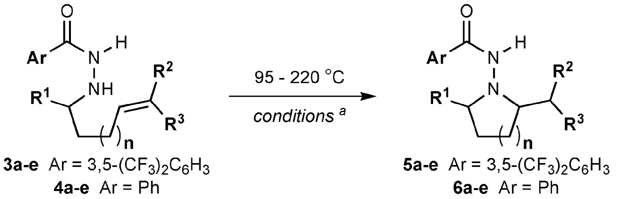
[a] Conditions: heated in $PhCF_3$ (0.05 M), in sealed tubes (18–40 h) or in a microwave reactor (10–16 h). [b] Isolated yield. [c] NMR yield using an internal standard. [d] Obtained as a mixture of diastereoisomers (see ESI‡).

intermolecular processes are more challenging (especially for alkenes).[12] With optimized reagents, we revisited previously unsuccessful attempts to achieve a metal-free intermolecular alkene hydrohydrazidation simply upon heating. The lead result obtained is shown in eqn (1).



(1)

Table 2 Scope of 3,5-bis(trifluoromethyl)benzhydrazides cyclizations

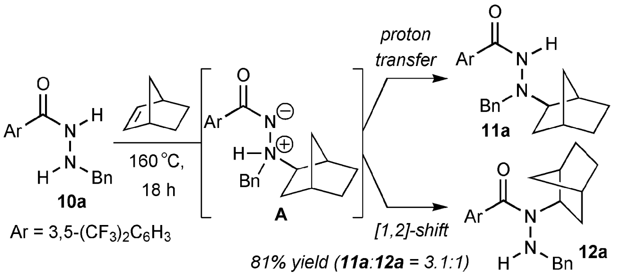


Entry	Substrate	Temp/°C	Product	Yield[b] (%)
1	**3a** $R^1 = R^2 = R^3 = H$ $n = 1$	95	**5a**	81
2	**4a**	120	**6a**	93
3	**3b** $R^1 = Me$, $R^2 = R^3 = H$ $n = 1$	95	**5b**	85[c]
4	**4b**	120	**6b**	98[c]
5	**3c** $R^1 = R^2 = H$, $R^3 = Me$ $n = 1$	150	**5c**	91
6	**4c**	175	**6c**	75
7	**3d** $R^1 = R^2 = R^3 = H$ $n = 2$	175	**5d**	82
8	**4d**	200	**6d**	90
9	**3e** $R^1 = R^3 = H$, $R^2 = Et$ $n = 2$	195	**5e**	53
10	**4e**	220	**6e**	51[d]

[a] Conditions: heated in $PhCF_3$ (0.05 M), in a microwave reactor (10–24 h). [b] Isolated yield. [c] NMR yield using an internal standard. [d] Obtained as a mixture of diastereoisomers (see ESI‡).

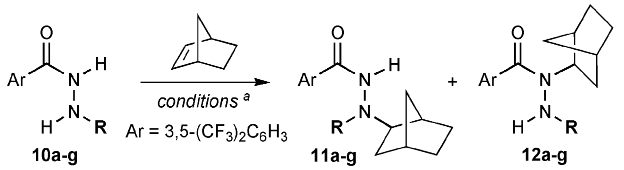
Encouragingly, a mixture of mono- (**8**) and bis-hydroamination (**9**) products was formed upon heating 3,5-bis(trifluoromethyl)benzhydrazide **7** with excess norbornene. Reasoning that this lack of control would be avoided with a substituted derivative, benzylic substrate **10a** was selected for further development. After optimization of solvent, concentration and equivalents of alkene (see ESI‡), hydroamination products **11a** and **12a** were obtained in 81% yield and 3.1 : 1 ratio. The two products are likely formed from a common ammonium ylide intermediate (**A**, see Scheme 2),[13] with the expected major product **11a** arising from a proton transfer and the minor product **12a** forming through a competing [1,2]-shift of the norbornyl group.[14] Such [1,2]-shifts are related to the Stevens' rearrangement and usually occur through a diradical mechanism.[15] The scope of this intermolecular reactivity was explored with several hydrazides, as shown in Table 3.

Encouragingly, the hydroamination of norbornene proved efficient with several alkylhydrazides, providing the hydroamination products in combined yields ranging from 74–87% (Table 3, entries 1–7). The presence of alkene and benzyl ether functionalities on the hydrazide was also well tolerated (entries 6 and 7). In all cases the expected hydroamination product **11** was favored over rearrangement product **12**, with the ratio of products showing little dependence on the size of the



Scheme 2 Intermolecular hydrohydrazidation: divergent reactivity from the ammonium ylide intermediate.

Table 3 Intermolecular hydrohydrazidation scope



Entry	Hydrazide (R)	Reaction time/h	Products	Yield[b] (%)/ ratio (**11** : **2**)
1	Bn	40	**11a** + **12a**	81 (3.1 : 1)
2	Me	17	**11b** + **12b**	85 (4.3 : 1)
3	*i*-Pr	17	**11c** + **12c**	74 (1.7 : 1)
4	*i*-Bu	17	**11d** + **12d**	73 (2.7 : 1)
5	*c*-C_6H_{11}	40	**11e** + **12e**	87 (3.2 : 1)
6	$(CH_2)_2CH{=}CH_2$	17	**11f** + **12f**	87 (3.7 : 1)
7	$(CH_2)_3OBn$	17	**11g** + **12g**	86 (3.3 : 1)

[a] Conditions: heated in $PhCF_3$ (2 M), 160 °C, sealed tube, 17–40 h. [b] Isolated yields.

hydrazide substituent (R). This observation indicates that proton transfer of the ammonium ylide intermediate is more facile than migration of the alkyl substituents. Importantly, no rearrangement product derived from [1,2]-shift of the R substituent was detected, highlighting the preference for the norbornyl substituent to migrate over several alkyl groups.

In summary, we have performed a systematic investigation of the hydroamination reactivity of hydrazides and related compounds, showing its generality in simple intramolecular systems. More reactive benzoic hydrazides were identified, and 3,5-bis(trifluoromethyl)benzhydrazides proved more efficient in several cyclizations and enabled intermolecular hydrohydrazidations. Extensions of this work to access more substituted ammonium ylides and to enable alkyne hydroamination are in progress and will be reported in due course.

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Notes and references

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8 Heating semicarbazides at higher temperatures (200 °C) results in the formation of aminoisocyanate intermediates, which can lead to alkene cycloadducts: see ref. 7*a*.

9 An aza-Cope elimination process of an ammonium ylide formed *via* proton transfer is suspected at higher temperatures. For related reactivity, see: D. G. Morris, B. W. Smith and R. J. Wood, *J. Chem. Soc., Chem. Commun.*, 1968, 1134.

10 See the ESI‡ for details.

11 Two (slow) competing side reactions have been observed with hydrazides at high temperatures: aza-Cope elimination (see ref. 9) and formation of the parent imine through elimination of 3,5-bis(trifluoromethyl)benzamide.

12 For general reviews on alkene hydroamination, see ref. 1*a* and *e*. Even in intramolecular cases, reactivity is usually only general for 5-membered cyclizations, and is diminished by alkene substitution. The near thermoneutral nature of alkene hydroamination provides an additional challenge for intermolecular hydroaminations: A. M. Johns, N. Sakai, A. Ridder and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 9306.

13 Such dipoles are also called aminimides. For a seminal review, see: W. J. McKillip, E. A. Sedor, B. M. Culbertson and S. Wawzonek, *Chem. Rev.*, 1973, **73**, 255.

14 The structure of **12** was confirmed through analysis of the products resulting from the cleavage (SmI_2) of the N–N bond. See ESI‡.

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