Intermolecular Cope-type hydroamination of alkynes using hydrazines†

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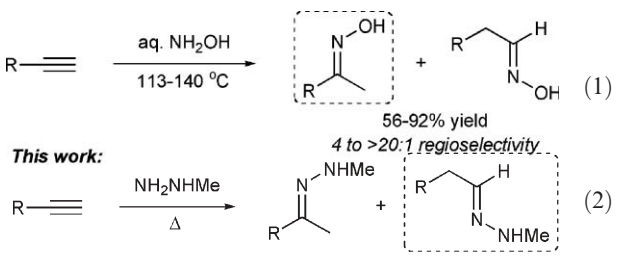
Metal-free, intermolecular hydroaminations are performed upon heating aryl acetylenes and $MeNHNH_2$ at 140 °C, with preferential formation of the linear, "anti-Markovnikov" hydrazones.

The addition of N–H bonds across unactivated alkenes and alkynes represents an efficient access to nitrogen-containing molecules.[1] Intermolecular hydroamination of alkynes provides a simple approach to imines and analogues, which are useful building blocks in organic synthesis. Due to the high activation energy associated with this reaction, most research efforts have focused on transition metal catalysis.[1,2] Notably, regioselective formation of aldimines or ketimines from terminal alkynes can be achieved upon selection of a catalyst possessing the appropriate steric and electronic tuning.[3] Despite the significant progress accomplished, there is still a need to develop methods that have different substrate scope and functional group compatibility, as well as alternate strategies to achieve regiocontrol.

Recently, we reported on a simple, metal-free intermolecular hydroamination procedure that involves heating aqueous hydroxylamine and alkynes (or alkenes).[4] With aliphatic and aromatic terminal alkynes, the addition is efficient and favours the formation of the ketoxime product with good selectivities (eqn (1)). Reasoning that the reaction occurs through a concerted, Cope-type, transition state (TS),[5] we speculated that the use of *substituted* hydroxylamines or hydrazines could destabilize this TS and lead to a change in regioselectivity. Herein, we report that hydrazines undergo a similar intermolecular hydroamination process and that the use of a substituted hydrazine, $MeNHNH_2$, favours the formation of "anti-Markovnikov" hydrazones (eqn (2)).[6]



(1)

(2)

Initial trials to extend the reactivity described in eqn (1) to hydrazines were performed using aqueous hydrazine and phenylacetylene. Encouragingly, 53% conversion to a 2.5 : 1 mixture of regioisomers favouring the "anti-Markovnikov" hydrazone was obtained in *i*-PrOH at 113 °C. Optimization of this lead result was performed with $MeNHNH_2$ and led to both increased conversions and regioselectivities, as shown in Table 1.

Initial screening of reaction conditions using phenylacetylene (**1a**) as substrate showed encouraging reactivity in various solvents (Table 1, entries 1–3), with protic solvents such as *i*-PrOH providing optimal conversion and regiocontrol for the formation of linear hydrazone **3a**. In general, the reaction is more efficient at high concentrations (1 M) and the use of distilled $MeNHNH_2$ under an inert atmosphere is beneficial. Due to its reduced reactivity compared to **1a**, optimization was continued using *para*-tolylacetylene (**1b**, entries 6–10). Gratifyingly, upon heating at 140 °C in *i*-PrOH for 18 h, good conversion and regioselectivity for the linear hydrazone **3b** was obtained (entry 9). With optimized conditions in hand, the substrate scope with respect to the alkyne could be evaluated. The results are presented in Table 2, which also features the derivatization of the linear hydrazone regioisomer to allow isolation by column chromatography.

As shown above, hydroamination of aromatic acetylenes using $MeNHNH_2$ proceeds in good conversions and good to excellent regioselectivity for the linear hydrazone products (**3a–j**). Substitution on the arene ring is generally well tolerated (entries 2–6 and 8), with the exception of 4-methoxyphenylacetylene which shows only modest reactivity (entry 7). In addition, heterocyclic acetylenes also react efficiently under these reaction conditions (entries 9 and 10).[7] In all cases, the semicarbazone derivative of the

Table 1 Optimization of the hydroamination using $MeNHNH_2$

1a R = H **1b** R = Me **2a-b** **3a-b**

Entry	R	Solvent	*T*/°C	Conversion (%) (**3** : **2**)[a,b]
1	H	Dioxane	113	22 (10 : 1)
2	H	DMSO-d_6	113	41 (5 : 1)
3	H	*i*-PrOH	113	87 (17 : 1)
4	H	*i*-PrOH	140	88 (14 : 1)
5	H	PhMe	140	26 (9 : 1)
6	Me	*i*-PrOH	113	34 (11 : 1)
7	Me	Dioxane	140	29 (4 : 1)
8	Me	DMSO-d_6	140	53 (6 : 1)
9	Me	*i*-PrOH	140	73 (8 : 1)
10[c]	Me	*i*-PrOH	140	24 (8 : 1)

[a] Conversions were determined by ^{1}H NMR of the unpurified reaction mixture using styrene as an internal standard. [b] Regioselectivity was determined by ^{1}H NMR. [c] 2 equiv. of $MeNHNH_2$ were used.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic characterization for all new products and computational details. See DOI: 10.1039/b715022a

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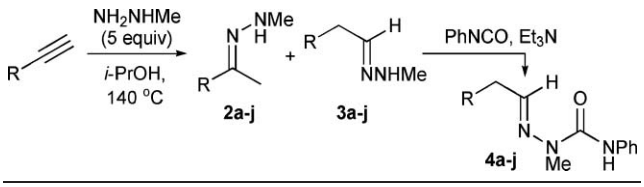
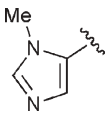
Table 2 Determination of substrate scope with different alkynes



Entry	R	Conversion (%) (**2** + **3**)[a]	Regioselectivity (**3** : **2**)[b]	Yield (**4**)[c] (%)
1	C_6H_5	87	14 : 1	58
2	2-MeC_6H_4	76	5 : 1	50
3	3-MeC_6H_4	77	15 : 1	49
4	4-MeC_6H_4	73	8 : 1	37
5	4-FC_6H_4	72	9 : 1	44
6	2-$MeOC_6H_4$	66	32 : 1	40
7	4-$MeOC_6H_4$	30	5 : 1	—
8	3,5-$(CF_3)_2C_6H_3$	77	10 : 1	31
9		76	25 : 1	55
10		81	6 : 1	45

[a] Determined by ^{1}H NMR of the unpurified reaction mixture using styrene as an internal standard. [b] Ratio determined by ^{1}H NMR. [c] Isolated yield after column chromatography.

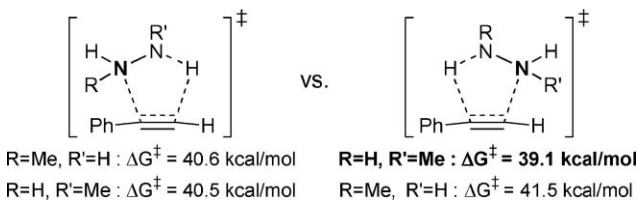


Fig. 1 Calculated activation energies associated with the four possible hydroamination TS.[8]

major regioisomer (**4a–j**) could be isolated after derivatization, in modest to acceptable yield (over two steps).

DFT calculations[8] were also performed to gain insight regarding a possible concerted mechanism[9,10] related to the Cope-type hydroamination reactivity of hydroxylamines.[4,5] In Fig. 1, the activation free energies ($\Delta G^{\ddagger}$) associated with the four possible concerted, five-membered, planar transition states (TS) are shown. As $MeNHNH_2$ is unsymmetrical, both nitrogen atoms can be involved in the C–N bond-forming event, which can occur also on both carbons of the alkyne. Using phenylacetylene as substrate, the TS minimizing steric interactions between the alkyne and hydrazine substituents, leading to the subsequent formation of the linear hydrazone **3a**, is favored by *ca.* 1.4 kcal mol^{-1}. These calculations are thus in good agreement with the observed regioselectivity (14 : 1).

In summary, we have developed a metal-free procedure for the intermolecular hydroamination of arylacetylenes using methyl hydrazine, which forms the "anti-Markovnikov", linear hydrazones in good yields and regioselectivities. Extension of the reactivity of hydrazines toward alkenes is underway and will be reported in due course.

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7 To date, trials with aliphatic (1-octyne), vinylic (1-ethynylcyclohexene) and internal (diphenylacetylene) alkynes have only showed minimal reactivity under similar reaction conditions.

8 Calculated free energies of TS in gas-phase at 298 K and 1 atm, relative to the free reactants, B3LYP/TZVP level of theory. See ESI† for a discussion regarding solvent effects and computational details.

9 For related examples of aza-Cope eliminations likely occurring through a similar transition state, see: (*a*) D. G. Morris, B. W. Smith and R. J. Wood, *Chem. Commun. (London)*, 1968, 1134–1135; (*b*) H. Posvic and D. Rogers, *J. Org. Chem.*, 1974, **39**, 1588–1589.

10 Control experiments performed with **1a**, $MeNHNH_2$ (5 equiv.) in *i*-PrOH (1 M) at 140 °C in the presence of AcOH (1 equiv.) or *i*-Pr_2NEt led to only slight decreases in total conversions (33 and 35%, respectively), suggesting alternative acid- or base-catalyzed mechanisms are not operating under the reaction conditions.