ChemPubSoc Europe

DOI: 10.1002/chem.201601560

CHEMISTRY A European Journal Full Paper

Organic Synthesis

Switchable [3+2] and [4+2] Heteroannulation of Primary Propargylamines with Isonitriles to Imidazoles and 1,6-Dihydropyrimidines: Catalyst Loading Enabled Reaction Divergence

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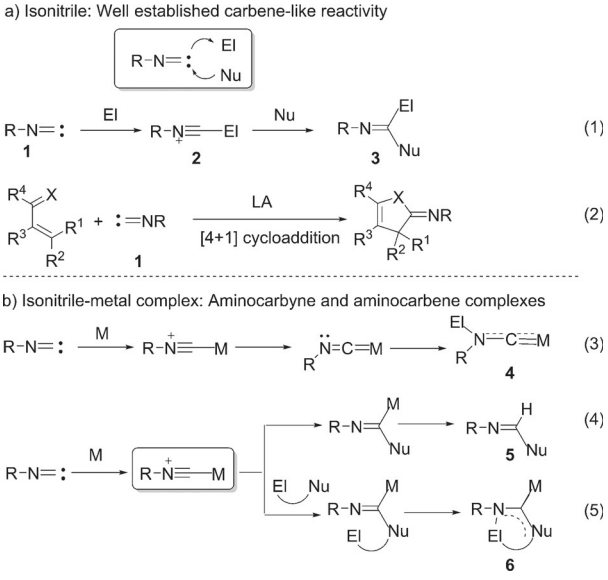
Abstract: Isonitrile **1** due to its carbene-like reactivity serves generally as a one-carbon synthon in a diverse set of organic transformations. We report in this article that the isocyano group can also act as a polarized triple bond to undergo, as a two-atom synthon, heteroannulation with primary propargylamines **15**. In addition, we serendipitously discovered that the reaction pathways can be modulated by simply changing the catalyst loading. In the presence of 0.1 equiv of $Yb(OTf)_3$ or TfOH, the reaction between **1** and **15** afforded exclusively imidazoles **16** by a formal [3+2] cycloaddition. At a higher catalyst loading ($Yb(OTf)_3$ (0.4 equiv) or TfOH (0.5 equiv)) under otherwise identical conditions, the same reaction furnished 1,6-dihydropyrimidines **17** in good to excellent yields by way of a formal [4+2] cycloaddition process. Mechanistic investigations indicated that both annulations went through an amidine intermediate resulting from the insertion of the isocyano group to the NH bond of the primary amine. Subsequent catalyst-loading-dependent 5-*exo*-dig or 6-*endo*-dig cyclization provided selectively the two heterocycles, respectively.

Introduction

The chemistry of isonitriles **1** has been dominated by the nucleophilic carbene-like reactivity of its divalent isocyano carbon. Indeed, it adds readily to an electrophile (e.g. carbonyl, imine, electron-deficient double bond, etc) to form a nitrilium intermediate **2** that can be trapped by a nucleophile to form an α-adduct **3** (Eq. (1), Scheme 1). The capacity of isonitrile to undergo an α-addition with both an electrophile and a nucleophile has been extensively exploited in the development of novel multicomponent reactions[1] ever since the discovery of the classic Passerini-3CR[2] and Ugi-4CR.[3] For the very same reason, the isocyano group acts generally as a one-carbon synthon in a broad range of [4+1],[4] [3+1],[5] [5+1],[6] and [2+2+1][7] cycloaddition reactions (Eq. (2), Scheme 1)[8] and radical-addition processes.[9]On the other hand, the isocyano group is also a strong two-electron donor ligand capable of forming complexes with a range of transition metals and its reactivity can be subsequently modulated by the nature of the metals. The coordination of isonitrile to electron-rich low-valent Group 6 and 7 elements with high π-electron releasing ability renders the isocyano nitrogen nucleophilic. In the presence of an electrophile, the N-alkylation occurs to provide aminocarbyne species **4** (M = Mo, W, Re, etc, Eq (3), Scheme 1).[10] When the coordination center is not a good π-electron donor and behaves as a good σ-electron acceptor (Lewis acid), the di-



Scheme 1. Modulable reactivity of the isocyano group.

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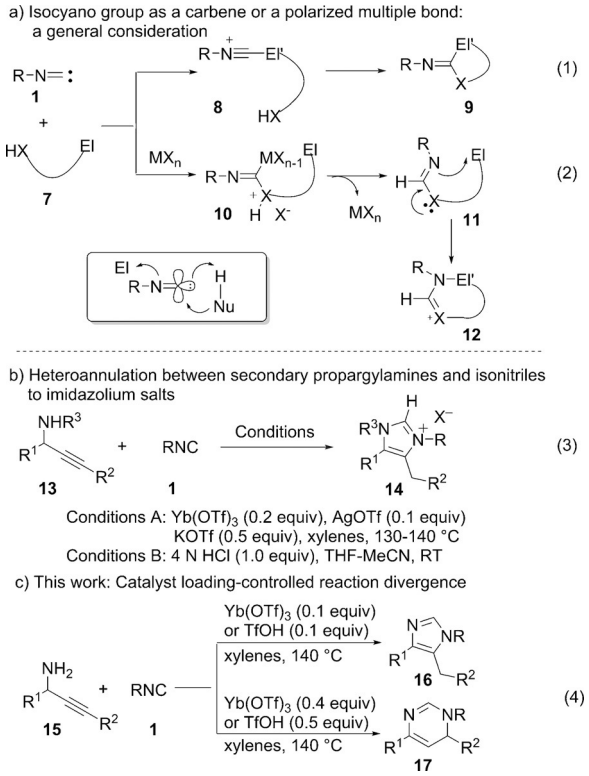
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201601560.

valent carbon atom of the ligated isonitrile becomes electrophilic and is susceptible to nucleophilic attack. With a pronucleophile NuH, insertion of isocyanide to Nu–H takes place to afford product **5** (e.g. M = Cu, Zn, Ag, lanthanide, etc, Eq. (4), Scheme 4).[11] With a nucleophile containing an electrophilic center, a sequence of reactions involving nucleophilic addition to the isocyano carbon followed by an intramolecular N-alkylation could occur to furnish a heterocyclic aminocarbene complex **6** (Eq (5), Scheme 1).[12] Both β-halo ethylamines (M = Pd, Pt, Au, etc)[13] and propargyl amines (M = Mn)[14] have been used as bifunctional substrates for the synthesis of NHC–metal complexes. In these transformations, both the terminal carbon and the internal nitrogen atoms of the isocyano group participated in the reaction by acting as an electrophilic and nucleophilic center, respectively. Therefore, the isocyano group reacted formally as a polarized triple bond. Notably, this unusual reactivity profile remained largely unexplored in organic synthesis.[15]

In connection with our long-standing interest in isocyanide chemistry,[16] we have recently initiated a research program aimed at exploiting the new reactivity of the isocyano group[17] and become particularly interested in the reaction of bifunctional substrates of type 7 containing both an acidic proton (XH) and an electrophilic center. Keto acids[18] and in situ formed imino acids[19] are typical reactants that have been exploited in the development of Ugi-type reactions. These reactions, initiated by nucleophilic addition of an isocyano carbon atom to the electrophilic center, followed by the classic α-addition pathway leading to **9** via the isonitrilium intermediate **8** (Eq. (1), Scheme 2). We hypothesized that if, in the presence of a suitable catalyst, the reaction of isonitriles **1** and substrates **7** can be initiated by insertion of isocyano group to the X–H bond leading to **10** and if the metal salt was chosen in such a way that the resulting C–M bond in **10** was prone to protolysis, then the formation of intermediate **11** with the concurrent regeneration of catalyst MX*n* might be expected. The final cyclization of **11** assisted by the lone pair of the heteroatom would produce heterocycle **12** (Eq (2), Scheme 2). Overall, the isocyano group would serve as a two-atom synthon in this heteroannulation process.

Indeed, we have very recently reported a synthesis of imidazolium **14** in which the isocyano group acted formally as a polarized triple bond, hence as a two-atom synthon, to undergo formal [3+2] cycloaddition with secondary propargylamines **13** (Eq. (3), Scheme 2).[20] In this multicatalytic process, three task-specific metal salts acted cooperatively to channel the reaction towards the formation of 1,3,4,5-tetrasubstituted imidazolium salts **14**. Ytterbium triflate catalyzed the insertion of isocyanide to the NH bond, silver triflate catalyzed the 5-*exo*-dig cyclization of the resulting propargyl amidines, and potassium triflate underwent salt metathesis with the hypothetical vinyl silver species to regenerate the catalytic species. Concurrently, Lavilla and co-workers[21] independently reported a hydrochloride-promoted heteroannulation between **1** and **13** to afford the same product **14**. In both cases, a secondary amine was used as a nucleophile to initiate the heteroannulation sequence. To enlarge the scope of this novel heteroannulation process, we set out



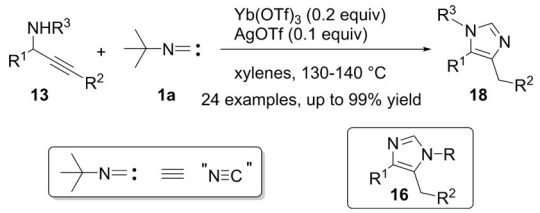
Scheme 2. Isocyanide as a polarized triple bond in heteroannulation reactions.

to examine the reaction between isonitriles **1** and primary propargylamines **15**. We serendipitously discovered that the reaction between **1** and **15** can be channeled towards the formation of either imidazoles **16** or 1,6-dihydropyrimidines **17** by simply adjusting the catalyst loading (Eq. (4), Scheme 2). In the presence of $Yb(OTf)_3$ or TfOH (0.1 equiv), the reaction of **1** with **15** afforded imidazoles **16** by way of a formal [3+2] heteroannulation process. By simply increasing the catalyst loading ($Yb(OTf)_3$ (0.4 equiv) or TfOH (0.5 equiv)), the same reaction provided 1,6-dihydropyrimidines **17** by a formal [4+2] cycloaddition. Mechanistic investigations indicated that both heteroannulations went through an amidine intermediate resulting from the insertion of isocyanide to the N–H bond of primary amines **15**. Subsequent 5-*exo*-dig or 6-*endo*-dig cyclization provided selectively the two different heterocycles.

Results and Discussion

Switchable [3+2] and [4+2] heteroannulation between isonitriles and primary propargylamines

Discovery and survey of reaction conditions: The imidazole nucleus is a structural motif found in many bioactive natural products, pharmaceuticals, and agrochemicals.[22] In spite of the existence of a number of synthetic methodologies,[22–24] the development of new and general methods of synthesis is still highly demanding.[25] In our preliminary studies, we have shown that the reaction between secondary propargylamines **13** and *tert*-butyl isonitrile (**1a**) in the presence of a catalytic



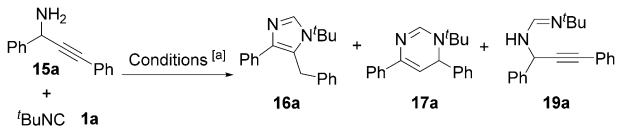
Scheme 3. N-Dealkylative heteroannulation between *t*BuNC (**1a**) and secondary propargylamine **13**.

amount of $Yb(OTf)_3$ (0.2 equiv) and AgOTf (0.1 equiv) afforded 1,4,5-trisubstituted imidazoles **18** resulting from the N-dealkylation of the initially formed imidazolium salt (Scheme 3). In this domino process, *t*BuNC (**1a**) served formally as a synthetic equivalent of "$^{+}$C=N^{-}". Based on our mechanistic assumption, we reasoned that the same reaction should afford directly the imidazoles without involving an N-dealkylation step if primary propargyl amines were used as reaction partners of isonitriles. Although this reaction will also give a 1,4,5-trisubstituted imidazoles **16**, the connectivity of the substituents in **16** will be different from that of **18**.

With this idea in mind, propargylamine **15a** and *tert*-butylisonitrile (**1a**) were chosen as test substrates for the survey of reaction conditions (Table 1). While no reaction occurred under thermal conditions (Table 1, entry 1), heating a solution of **1a** and **15a** in xylenes at 90 °C in the presence of ytterbium triflate ($Yb(OTf)_3$, (0.2 equiv)) afforded the NH insertion product **19a** (entry 2).[20,26] Increasing the reaction temperature to 120 °C provided cleanly imidazole **16a** and 1,6-dihydropyrimidine **17a** in a one-to-one ratio (entry 3). The formation of **17a** was surprising since this compound was never observed in the reaction of secondary propargylamines **13** with isonitriles **1**. It is nevertheless of high interest since dihydropyrimidines, aza-analogues of dihydropyridines, are of significant medicinal importance[27] and only a limited synthetic methodology has been developed for their synthesis.[28] Therefore, we set out to optimize conditions to drive the reaction towards the formation of either imidazole **16a** or 1,6-dihydropyrimidine **17a**.

It was quickly found that the ratio of **16a** and **17a** depended on the catalyst loading and reaction temperature (Table 1, entries 4 to 8). Performing the reaction in the presence of 0.4 equivalents of $Yb(OTf)_3$ at 140 °C provided compound **17a** exclusively in 86% yield (entry 7). On the other hand, with 0.1 equivalents of $Yb(OTf)_3$, the same reaction furnished **16a** as a major product in 63% isolated yield (entry 8). Further screening of catalysts indicated that TfOH was equally effective in catalyzing the heteroannulation of **1a** with **15a** in two different ways as $Yb(OTf)_3$.[29] With lower loading of TfOH (0.1 equiv), **16a** was isolated in 73% yield together with a trace amount of **17a** (entry 9). Increasing the loading of TfOH to 0.5 equiv, 1,6-dihydropyrimidine **17a** was formed in 78% isolated yield (entry 13).[30] It is worth noting that both Lavilla[21] and Hulme[31] have previously demonstrated that acid-catalyzed isocyanide insertion into the NH bond, while effective with anilines, failed with aliphatic amines. Finally, tributylammonium triflate ($nBu_3NH + TfO^{-}$), a white solid easily prepared from nBu_3N and TfOH, was also able to catalyze the [2+3] heteroannulation between **1a** and **15a** (entry 14). On the other hand, tetrabutylammonium triflate was devoid of catalytic activity (entry 15).

Table 1. Survey of conditions for heteroannulation between **1a** and **15a**: Catalyst-loading-dependent reaction divergence.

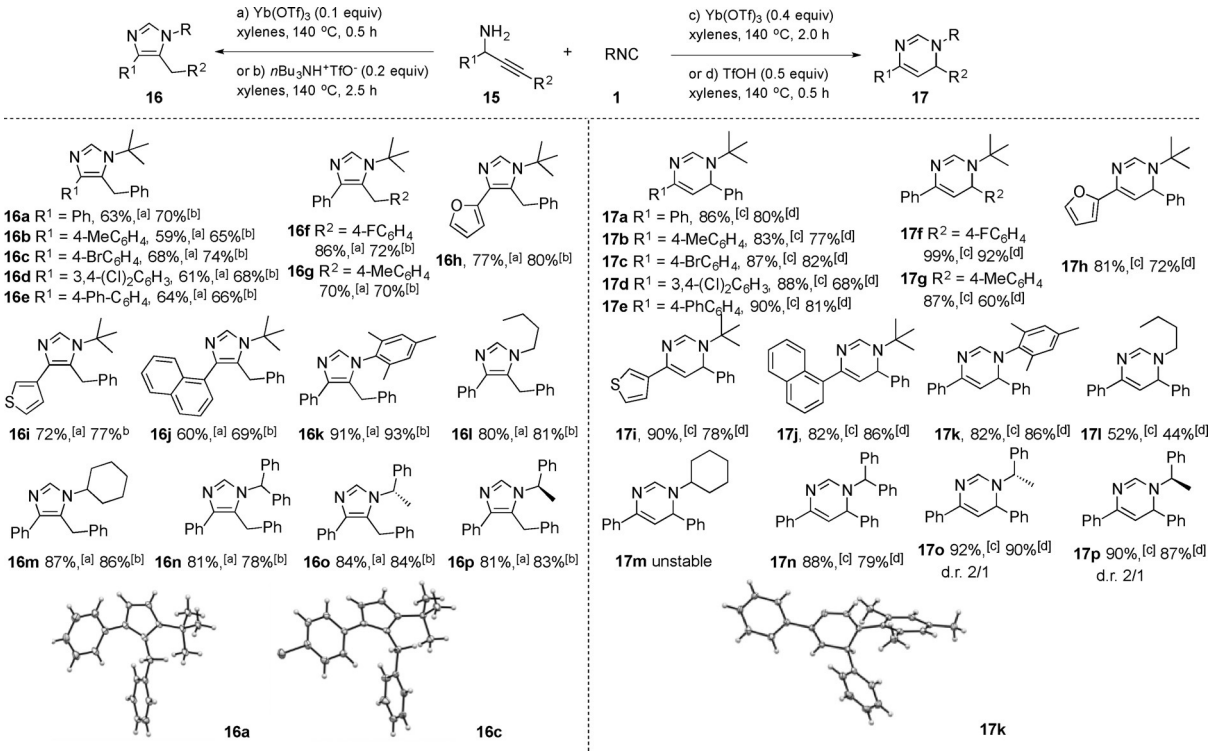


Entry	Cat. (equiv)	T [°C]	t [h]	**16a** [%][b]	**17a** [%][b]
1	–	120	12	0	0
2	$Yb(OTf)_3$ (0.2)[c]	90	8	trace	trace
3	$Yb(OTf)_3$ (0.2)	120	2	50	50
4	$Yb(OTf)_3$ (0.2)	130	2	40	60
5	$Yb(OTf)_3$ (0.2)	140	1	35	65
6	$Yb(OTf)_3$ (0.3)	140	1	17	83
7	$Yb(OTf)_3$ (0.4)	140	2	trace	86[d]
8	$Yb(OTf)_3$ (0.1)	140	1.5	63[d]	trace
9	TfOH (0.1)	140	0.5	73[d]	trace
10	TfOH (0.2)	140	0.5	70	15
11	TfOH (0.3)	140	0.5	55	31
12	TfOH (0.4)	140	0.5	34	56[d]
13	TfOH (0.5)	140	0.5	trace	78[d]
14	$nBu_3NH^{+}OTf^{-}$ (0.2)	140	2.5	70[d]	0
15	$nBu_4N^{+}OTf^{-}$ (0.2)	140	2.5	0	0

[a] Reaction conditions: **15a** (0.2 mmol), **1a** (0.4 mmol), catalyst, xylenes (c = 0.1 M). [b] NMR yield unless otherwise specified. [c] Only insertion product **19a** was formed. [d] Isolated yield.

Scope of catalyst loading-dependent [3+2] and [4+2] cycloadditions between primary propargylamines 15 and isonitriles 1

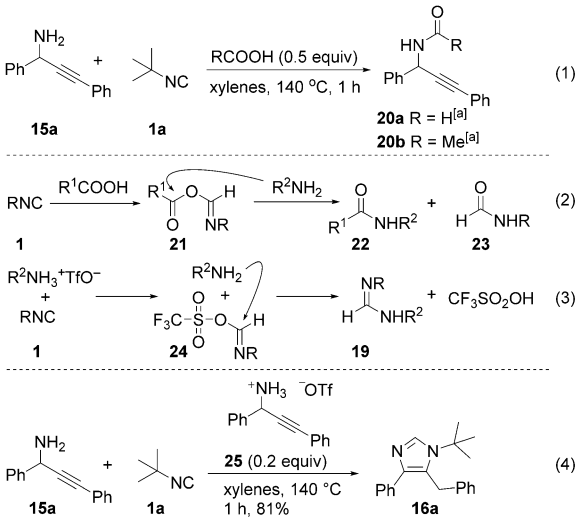
With the optimum conditions in hand, the generality of this catalyst loading controlled heteroannulation processes was investigated. For the sake of convenience, $nBu_3NH^{+}TfO^{-}$ (0.2 equiv) was used instead of TfOH for the synthesis of imidazole. As it is shown, imidazoles **16** and 1,6-dihydropyrimidines **17** (Scheme 4) with different substituents were easily accessible from the same starting materials by simply varying the catalyst loading. The reaction is not sensitive to the electronic properties of the R^1 and R^2 groups and most importantly, primary, secondary, tertiary alkyl, and aryl isocyanides were all accepted substrates. Both (*S*)- and (*R*)-α-methyl benzyl isocyanides participated in the reaction to afford imidazoles (**16o**, **16p**) or 1,6-dihydropyrimidines (**17o**, **17p**, d.r. = 2:1). For the [2+3] heteroannulation of **1** with **15**, the reaction catalyzed by $nBu_3NH^{+}OTf^{-}$ (0.2 equiv) afforded in general better yields of imidazoles than those catalyzed by $Yb(OTf)_3$ (0.1 equiv), whereas for the [2+4] heteroannulation of **1** with **15**, higher yields of 1,6-dihydropyrimidines were obtained using $Yb(OTf)_3$ (0.4 equiv) as a catalyst. The structures of compounds **16a**, **16c**, and **17k** were confirmed by X-ray crystallographic analysis.[32]



Scheme 4. Catalyst-loading-dependent heteroannulation of primary propargylamines with isonitriles: Scope of [3+2] and [4+2] cycloadditions.

Mechanistic studies

Control experiments were performed to gain insights into the reaction mechanism. Reaction of **1a** and **15a** in the presence of formic acid or acetic acid (0.5 equiv) under otherwise identical conditions afforded as major products the N-acylated products **20a** (R = H) and **20b** (R = Me), respectively (Eq. (1), Scheme 5). Neither imidazole **16a** nor 1,6-dihydropyrimidine**17a** was formed under these conditions. While the transformation depicted in Equation (1) is known and can be explained by the N-acylation of amines **15** by the in situ generated formimidate carboxylate mixed anhydride (FCMA) **21** (Eq. (2), Scheme 5),[33] the triflic acid-catalyzed NH-insertion of amine to isocyanide, to the best of knowledge, is unknown. We reasoned that the same type of intermediate **24**, reminiscent of FCMA **21** (Eq. (3), Scheme 5) is also formed and that the primary amine, being a soft nucleophile, would attack preferentially the imidate carbon atom leading to amidine **19**.[34] Being one of the strongest organic acids (p*K*a (H_2O) = −14), TfOH will protonate the primary amines **15**, upon mixing, leading to ammonium salts. Therefore, the reaction mixture would be only weakly acidic. Indeed in the absence of amine, *t*BuNC polymerized rapidly upon addition of TfOH (0.5 equiv) at room temperature. The fact that $nBu_3NH^+OTf^-$ was also capable of catalyzing the same transformation led us to hypothesize that the true catalyst might be in fact the ammonium salt formed in situ from propargylamines and TfOH. Indeed, the triflate salt **25** derived from propargylamine **15a** can catalyze the reaction of **15a** with **1a** to afford **16a** in 81% yield (Eq. (4), Scheme 5).



Scheme 5. Results of control experiments. [a] Yield was not determined.

Since we have shown that amidine **19a** is a common intermediate for both heterocycles **16a** and **17a**, it is reasonable to assume that these two heterocycles are formed by 5-*exo*-dig and 6-*endo*-dig cyclizations of **19a**, respectively. While both processes are in principle allowed according to Baldwin's rule,[35] the formation of a five-membered ring is generally preferred kinetically, although it is known that both the substrate structures and the reaction conditions can alter the regioselectivity.[36] As a matter of fact, regioselective cyclization of structurally related substrates such as 2-alkynyl benzoic acid **26**,[37] 2-alkynyl benzamides **27**,[38] propargyl ureas **28**,[39] and prop-

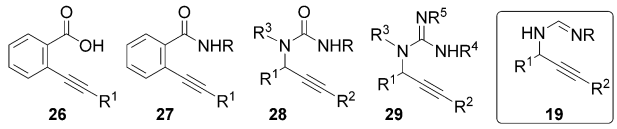
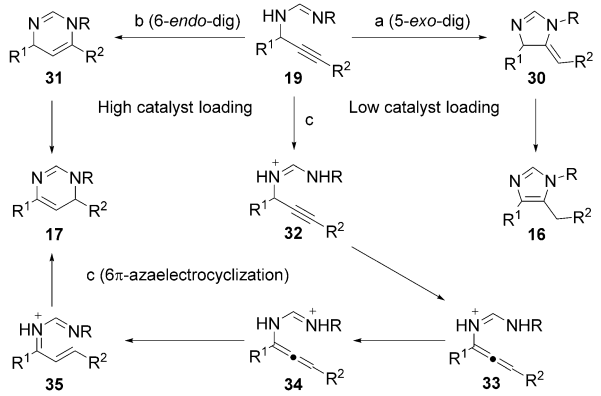


Figure 1. Amidines and related substrates.

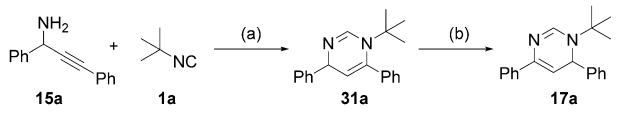
argyl guanidines **29**[40] has been extensively studied and conditions have been established for performing either a 5-*exo*-dig or a 6-*endo*-dig cyclization (Figure 1). However, the cyclization of amidine **19** has been far less investigated and to the best of our knowledge, only 5-*exo*-dig cyclization leading to imidazole is known.[20,21,24d,e] Indeed, in this case, the 5-*exo*-dig cyclization furnishes an aromatic compound **16** after facile double-bond isomerization of the primary cyclization product **30**, providing, therefore, additional thermodynamic driving force (pathway a, Scheme 6).[41]



Scheme 6. Possible reaction pathways to imidazoles **16** and 1,6-dihydropyrimidine **17**.

While 6-*endo*-dig cyclization of amidine **19** to **31** followed by double-bond isomerization could explain the formation of 1,6-dihydropyrimidine **17** (pathway b, Scheme 6), there could be an alternative pathway to account for the formation of 1,6-dihydropyrimidine **17** (pathway c). Protonation of amidine **19** would afford amidinium **32** which could subsequently isomerize to allene **33** due to the increased acidity of the propargylic CH in **32**.[42] Two further isomerization steps would convert **33** to triene **35** via intermediate **34**. A 6π-azaelectrocyclization of **35** would then afford directly the 1,6-dihydropyrimidine **17** (pathway c, Scheme 6).[43,44]

To differentiate pathways b and c, the reaction between **1a** and **15a** leading to **17a** was re-examined in detail. Gratefully, we were able to isolate 1,4-dihydropyrimidine **31a** in 87% yield by rapidly extracting the aqueous work-up solution and confirmed that **31a** was readily isomerized to thermodynamically more stable form **17a** in the presence of a weak base such as $NaHCO_3$ (Scheme 7). This result clearly indicated that **17a** was most probably formed by a 6-*endo*-dig cyclization rather than the 6π-azaelectrocyclization pathway. Nevertheless,



Scheme 7. Isolation of 1,4-dihydropyrimidine and its isomerization to 1,6-dihydropyrimidine. Conditions: a) $Yb(OTf)_3$ (0.4 equiv), xylenes, 140 °C; b) Saturated aqueous $NaHCO_3$, RT, 5 min.

at the present stage, we do not have a clear-cut explanation on how the catalyst loading switched the reaction pathways.

Conclusion

In summary, we have developed a novel synthesis of two important heterocycles from the same propargylamines and isonitriles. In these heteroannulation reactions, the isocyano group served formally as a polarized multiple bond, hence a two-atom synthon, while the primary propargylamine acted either as a three or four-atom synthon to undergo the [3+2] or [4+2] heteroannulation with isonitrile. While the switchable catalyst-controlled selective generation of different products from the same starting materials has attracted attention of chemists for years, the intriguing catalyst loading enabled reaction divergence reported here added yet another dimension to the field of diversity-oriented synthesis.[45]

Experimental Section

For details of the synthetic procedures, physical and spectroscopic data, copies of ^1H, ^{13}C NMR spectra of compounds, see the Supporting Information.

General procedure for the synthesis of imidazole 16

Conditions A: $Yb(OTf)_3$ (12.0 mg, 0.02 mmol, 0.1 equiv), propargylamine **15** (0.2 mmol), isonitrile **1** (0.4 mmol), and xylenes (2.0 mL) were loaded into a sealed tube. The resulting mixture was heated to 140 °C and stirred for 0.5 h. After completion of the reaction, the solution was quenched with sat. aq. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified by flash column chromatography to afford imidazole **16**.

Conditions B: $nBu_3HN^{+-}OTf$ (13.0 mg, 0.04 mmol, 0.2 equiv), propargylamine **15** (0.2 mmol), isonitrile **1** (0.4 mmol), and xylenes (2.0 mL) were loaded into a sealed tube. The resulting mixture was heated to 140 °C and stirred for 2.5 h. After completion of the reaction, the solution was quenched with sat. aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified by flash column chromatography to afford imidazole **16**.

General procedure for the synthesis of 1,6-dihydropyrimidine 17

Conditions C: $Yb(OTf)_3$ (50.0 mg, 0.08 mmol, 0.4 equiv), propargylamine **15** (0.2 mmol), isonitrile **1** (0.4 mmol), and xylenes (2.0 mL) were loaded into a sealed tube. The resulting mixture was heated to 140 °C and stirred for 2 h. After completion of the reaction, the solution was quenched with sat. aq. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified by flash column chromatography to afford dihydropyrimidine **17**.

Conditions D: TfOH (15.0 mg, 9.0 μL, 0.1 mmol, 0.5 equiv), propargylamine **15** (0.2 mmol), isonitrile **1** (0.4 mmol), and xylenes (2.0 mL) were loaded into a sealed tube. The resulting mixture was heated to 140 °C and stirred for 0.5 h. After completion of the reaction, the solution was quenched with sat. aq. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed in vacuo and the residue was purified by flash column chromatography to afford dihydropyrimidine **17**.

Acknowledgements

Financial support from EPFL (Switzerland), Swiss State Secretariat for Education and Research (SER), the Swiss National Science Foundation (SNSF), and National Natural Science Foundation of China are gratefully acknowledged. We thank Dr. R. Scopelliti for X-ray crystallographic analysis.

Keywords: dihydropyrimidine · heteroannulation · imidazoles · insertion · isonitriles · propargylamine

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Received: April 4, 2016
Published online on May 3, 2016