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Synthesis of α-CN and α-CF_3 N-Heterocycles through Tandem Nucleophilic Additions

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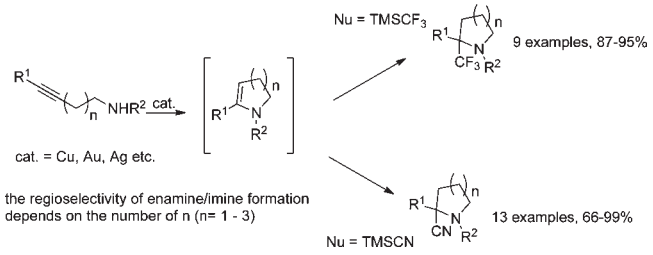
ABSTRACT



Using a readily available secondary aminoalkyne as starting material, a powerful strategy was discovered to prepare precursors of biologically important unnatural cyclic aminoacids and fluorinated N-heterocycles with important ring sizes (e.g., 5–7) in a one-pot reaction using two nucleophilic additions in a tandem fashion.

N-Heterocycles of different ring sizes and substitution patterns are among the most important structural classes in medicinal chemistry. Among them, 5-, 6-, and 7-membered rings are the most common.[1] Recently, we reported the synthesis of functionalized 5-, 6-, and 7-membered N-heterocycles, via a Cu(I)-catalyzed, one-pot, tandem hydroamination/alkynylation, a process we called cyclization-triggered addition.[2] We wanted to investigate if this protocol could be extended to the tandem addition of two different nucleophiles to an alkyne, beginning with an intramolecular hydroamination of aminoalkyne **1** and ending with the addition of a second nucleophile to the in situ generated enamine or imine. We are now pleased to report that our one-pot cyclization-triggered addition furnishes α-CN and α-CF_3 substituted N-heterocycles in very good to excellent yields.

Literature reports on tandem additions of two different nucleophiles to an alkyne in one pot are indeed rare.[3] For example, Li and co-workers reported the tandem addition of an amine and alkyne to α,β-unsaturated esters through a proposed iminium intermediate.[4] Che and co-workers have reported a gold(I) catalyzed tandem synthesis of pyrrolo-[1,2-a]quinolones.[5] A gold catalyzed one-pot synthesis of 1,2-dihydroquinoline derivatives from amines, internal alkynes, and terminal alkynes has also been reported by Bertrand and co-workers.[6] Finally, Schafer and co-workers have reported a titanium catalyzed one-pot synthesis of α-aminoacids from terminal alkynes.[7]

We used the reaction of aminoalkyne **1a** and TMS-CN **(2a)** as our initial model because the reported synthesis of α-cyano-N-heterocycles—oxidative cyanation of a cyclic tertiary amine[8]—often suffer from limited scope and lack of regioselectivity. Using 5% CuBr as catalyst, our tandem reaction gives 30% of the desired product **3a** with excellent regioselectivity (Table 1, entry 1). When the reaction is carried out at higher temperature under microwave condition the yield of **3a** is excellent (Table 1, entry 2). Gold also works well in this reaction (Table 1, entry 3). Under microwave

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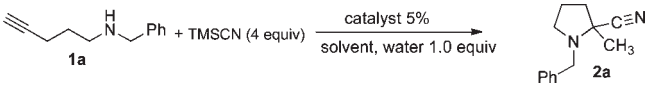
condition, the Cu(I)-catalyzed reaction is very fast (30 min), but conventional heating also works very well if longer reaction times are employed (Table 1, entry 4). Increasing the scale of this reaction did not reduce the yield of product.

Table 1. Screening for the Best Conditions for a Tandem Amination/Cyanation

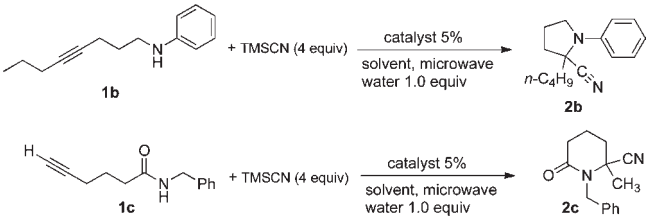


entry	catalyst	solvent	temp, time	yield %
1	CuBr	dioxane	rt, 12 h	30
2	CuBr	dioxane	mw[a], 100 °C, 0.5 h	95
3	IPrAuCl/AgOTf	dioxane	mw[a], 100 °C, 0.5 h	90
4	CuBr	dioxane	100 °C, 12 h	92
5	CuBr	toluene	mw[a], 100 °C, 0.5 h	90
6[b]	CuBr	dioxane	mw[a], 100 °C, 0.5 h	82

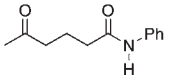
[a] mw = microwave. [b] Using 10 equiv of water; IPrAuCl = Chloro-[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I).

With optimized condition in hand, we turned our attention to less basic amines (Table 2).

Table 2. Screening for the Best Conditions for a Tandem Amination/Cyanation Using Less Basic Aminoalkynes



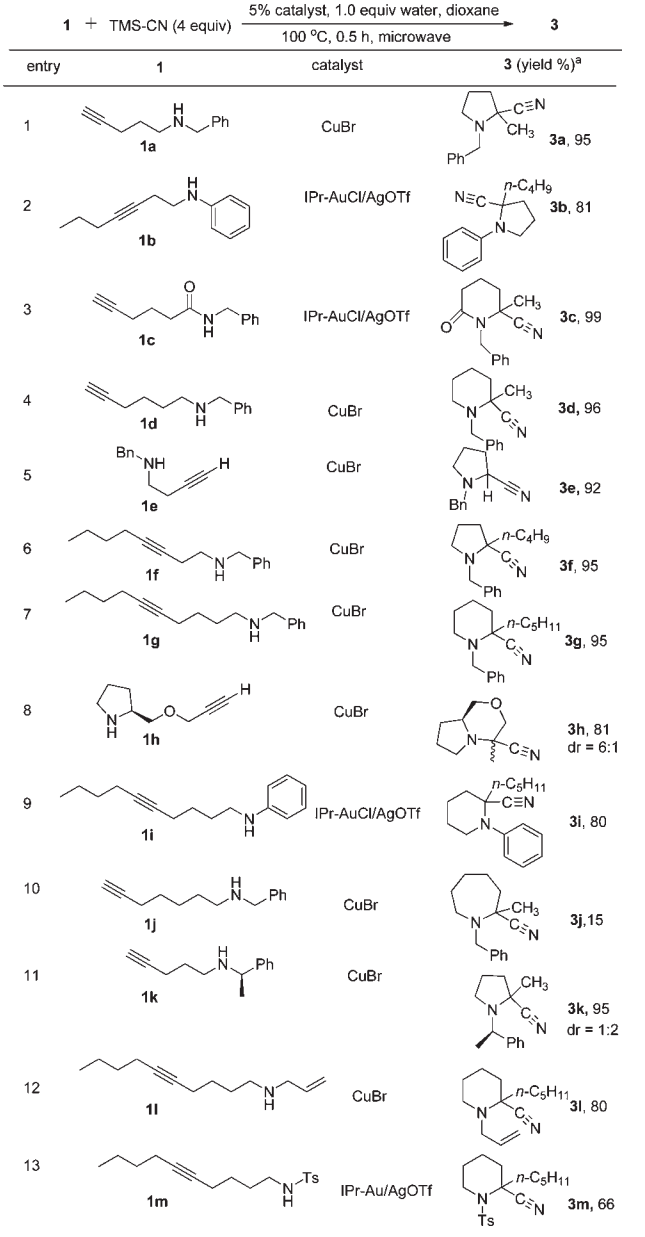
entry	1	catalyst	temp, time	yield%
1	**1b**	CuBr	mw, 100 °C, 40 min	0[a]
2	**1b**	IPrAuCl/AgOTf	mw, 100 °C, 40 min	81
3	**1c**	CuBr	mw, 100 °C, 40 min	0
4	**1c**	IPrAuCl/AgOTf	mw, 100 °C, 40 min	99

[a]  was isolated as major product (80%)

The aromatic amine tethered alkyne **1b** gave mostly the hydration product (Table 2, entry 1). We then decided to use a gold catalyst, IPrAuCl/AgOTf), capable of strong alkyne activation and with good thermal stability; this catalyst gave the desired product in excellent yield (Table 2, entry 2). We obtained similar results using the amide tethered alkyne **1b** (Table 2, entries 3 and 4).

The scope of the tandem amination/cyanation sequence is outlined in Table 3. This reaction worked extremely well in all cases giving near-quantitative chemical yields of 5-, and 6-membered rings. Complete regioselectivity was observed in all cases.

Table 3. Scope of the Tandem Amination/Cyanation Process



The regioselectivity obeyed Baldwin's rules,[9] that is, cyclization of 4-yn-amine **1a** and 3-yn-amine **1b** gave five-membered ring products through 5-endodig and 5-exodig processes whereas the reaction of 5-yn-amine (e.g., **1g**) produced a six-membered ring through a 6-exodig process, and the reaction of 6-yn-amine (e.g., **1j**) furnished a seven-membered ring through a 7-exodig process. When a chiral aminoalkyne was used (**1h**), a moderate chiral induction was observed (dr = 1:6, Table 3, entry 8).

Encouraged by the success of the tandem amination/cyanation sequence, we turned our attention to the synthesis

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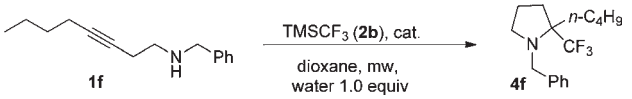
of trifluoromethylated N-heterocycles, a medicinally important class of compounds[10] whose synthesis usually requires multisteps.[10,11] Simply by reacting our in situ generated enamine intermediate with a nucleophilic CF_3 source, our protocol would lead to a one-pot synthesis of a CF_3-containing N-heterocycle. We used the reaction of aminoalkyne **1f** and TMS-CF_3 to optimize reaction conditions. Using 5% CuBr as catalyst, we observed none of the desired product **4a** (Table 4, entry 1); this result is reasonable if one realizes that TMS-CF_3 is a rather inert reagent unless a suitable activator is present (i.e., a fluoride source to cleave the TMS group). Although CsF was not successful (Table 4, entry 2), either copper or gold catalysts, in combination with AgF, produced very good yields of **4a** (Table 4, entries 3 and 4). CuF_2 also furnished the desired product, albeit in low yield (Table 4, entry 5). Because both gold and copper worked equally well, we suspected that the real catalyst was AgF. Indeed, we found this to be the case (Table 4, entry 8). The optimized loading of AgF was found to be 1.5 equiv (Table 4, entry 9). Higher temperatures have a deleterious effect on the yield of **4** (Table 4, entry 11), and the reaction proceeded well even at room temperature, although longer times were needed (Table 4, entry 12).

Table 4. Screening for the Best Condition for Tandem Amination/Trifluoromethylation Sequence[a]

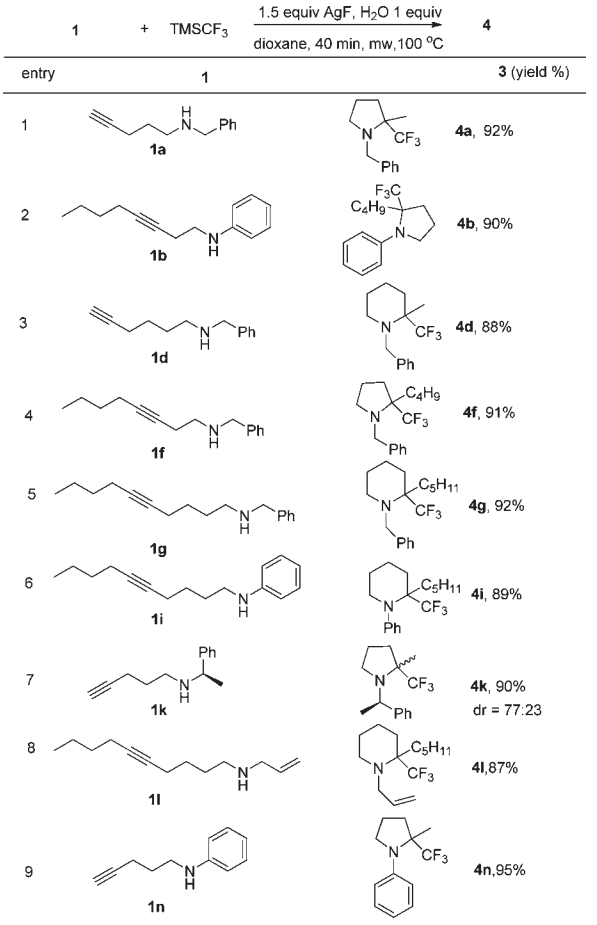


entry	catalyst	temp °C	time	yield %
1	CuBr (5%)	100	40 min	0
2	CuBr (5%)/CsF (1.0 equiv)	100	40 min	0
3	IPrAuCl (5%), AgF (1.0 equiv)	100	40 min	80
4	CuBr(5%)/AgF(2.0 equiv)	100	40 min	82
5	CuF_2 (2.0 equiv)	100	40 min	15
6	AgF (2.0 equiv)	100	40 min	90
7	AgF (0.2 equiv)	100	40 min	40
8	AgF (1.0 equiv)	100	40 min	70
9	AgF (1.5 equiv)	100	40 min	91
10	AgF (4.0 equiv)	100	40 min	82
11	AgF (1.5 equiv)	120	40 min	82
12	AgF (1.5 equiv)	rt	6 h	88

[a] mw = microwave; IPrAuCl = Chloro[1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene]gold(I).

The scope of our tandem amination/trifluoromethylation reaction is outlined in Table 5. The reaction worked extremely well in all cases giving near-quantitative chemical yields of five-, and six-membered rings. Complete regioselectivity was observed and its regioselectivity also obeyed Baldwin's rules. When a chiral aminoalkyne was used (**1k**), a moderate chiral induction was observed (dr = 77:23, Table 5, entry 7). It should be noted that AgF worked equally well with basic aliphatic aminoalkynes and less basic aromatic aminoalkynes.

Table 5. Tandem Amination/Trifluoromethylation Process



To determine the nucleophilic intermediate in the tandem amination/trifluoromethylation process, we monitored this reaction by ^{19}F NMR and ^{1}H NMR under similar conditions to those used in Table 2 (but using CD_3CN as solvent because of its better dissolving properties toward the silver salt). Five minutes into the reaction we observed a peak ascribed to CF_3Ag in ^{19}F NMR (δ −25.5, d, J^2_{F-Ag} = 94 Hz),[12] together with a signal corresponding to CF_3H in ^{19}F NMR (δ −79.9, d, J^2_{F-H} = 79 Hz) and ^{1}H NMR (δ 6.70, d, J^2_{F-H} = 79 Hz). The formation of CF_3H can be explained by protodemetalation of the CF_3Ag intermediate. Thus, it is highly likely that CF_3Ag is the real nucleophilic species in the reaction.[12]

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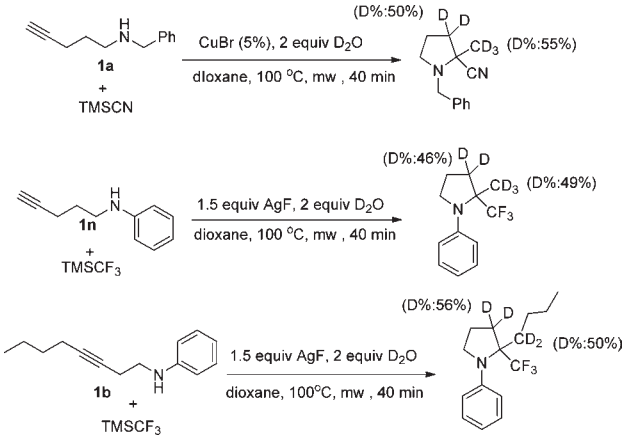
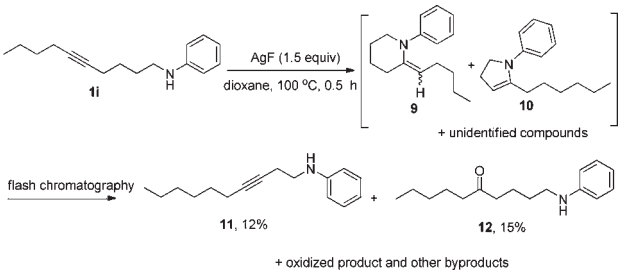
We conducted deuterium experiments to explore further the mechanism of this tandem process (Scheme 1). For both, tandem amination/cyanation and tandem amination/trifluoromethylation reactions, deuterium was detected on the ring carbon as well as on the exocyclic carbon. These results indicate that the proposed enamine intermediate probably undergoes additional transformations like retrohydroamination or tautomerization before the second nucleophilic attack takes place.

Scheme 1. Deuterium Experiments on Amination/Cyanation and Amination/Trifluoromethylation Reactions



To verify the above enamine formation mechanism, we investigated the reaction of **1i** in the absence of a second nucleophile (Scheme 2). Without a second nucleophile, the reaction of **1i** produces a relatively complex mixture; its NMR spectrum signaled the presence of enamine intermediates and other byproduct. We tentatively assigned the structure of the enamine intermediates as **9** and **10**. Silica gel flash chromatography of this reaction mixture gave products **11** and **12**.

Scheme 2. Reaction of **1i** in the Absence of a Second Attacking Nucleophile



Because **11** and **12** are not detected in the reaction mixture prior to silica gel chromatography, their formation can only be explained by invoking hydration of the corresponding enamines during chromatography. This experiment not only confirms the role of enamine as intermediate, but also underscores the importance of having a second attacking nucleophile (i.e., the tandem sequence) for a clean reaction to take place. Furthermore, the isolation of **11** implies that the hydroamination is indeed reversible. Although enamine is generally considered a nucleophile, in the presence of a suitable catalyst like copper, it can function as an electrophile.[13]

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Supporting Information Available. Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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