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COMMUNICATIONS

Published on Web 09/01/2006

Catalytic One-Pot Synthesis of Cyclic Amidines by Virtue of Tandem Reactions Involving Intramolecular Hydroamination under Mild Conditions

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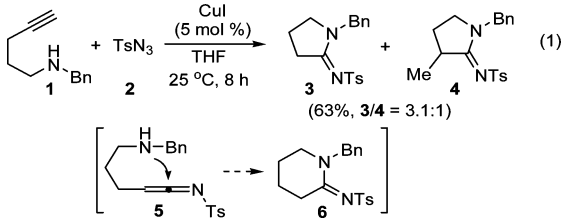
A range of multicomponent reactions, especially consisting of multiple reversible steps, are often favorably driven by a certain irreversible step to facilitate the whole transformation.[1] For example, release of stable molecules such as N_2, CO, or CO_2 can serve as a driving force, thereby enabling the reactions to be carried out under mild conditions. Recently, we have reported highly efficient Cu-catalyzed three component reactions,[2] in which terminal alkynes and sulfonyl azides are coupled with amines, alcohols, and water to give amidines, imidates, and amides, respectively. Although the mechanistic details are not fully described yet, it is presumed to proceed via a ketenimine intermediate, which has been also proposed by Fokin et al.[3]

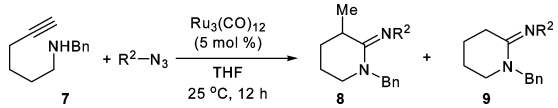
To expand the scope of these novel couplings, we envisioned that the reaction of 1,*n*-aminoalkynes with sulfonyl azides could provide cycloamidines,[4] which are highly useful in medicinal and coordination chemistry as well as materials science.[5] When 1-(*N*-benzyl)amino-4-pentyne (**1**) was treated with TsN_3 (**2**), to our surprise, 5-membered amidines were obtained as a mixture of **3** and **4** using CuI catalyst (eq 1). The outcome was unexpected in that the intramolecular attack of amino group into the putative tethered ketenimine (**5**) should lead to a six-membered amidine (**6**) if it follows the same pathway as in the intermolecular version.



We immediately found that several significant differences exist between the inter- and intramolecular reactions. First, whereas only a few copper salts, representatively CuI, perform the interreactions, the intramolecular version could be catalyzed with a range of metal species including Pd(II), Pt(II), Au(III), Ru(0, III) as well as Cu(I), although the catalytic activity and selectivity were dependent on the metals employed.[6] Among those, $Ru_3(CO)_{12}$ displayed notably high efficiency in THF. Second, while sulfonyl azides were the only efficiently viable substrates in the interreactions, a range of electron-deficient azides readily participated in the intraversion of amidine synthesis (Table 1).

When 1,5-aminoalkyne (**7**) was reacted with *p*-toluenesulfonyl azide at ambient temperature, two cycloamidine products **8** and **9** (8.0:1) were produced in high yield by virtue of $Ru_3(CO)_{12}$ (entry 1).[7] The yield was slightly improved by the presence of Et_3N while the selectivity was not significantly changed (entry 2). The reaction proceeded smoothly with various sulfonyl azides (entries 3−4). Noticeably, only one compound **8** having a α-methyl group was produced exclusively in good yields when **7** was reacted with

Table 1. Scope of Azides in the Reaction with Aminoalkyne **7**[a]



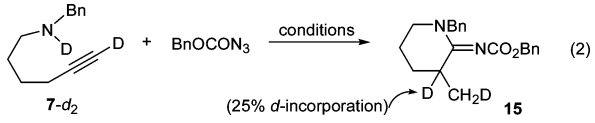
entry	R^2	ratio (**8**/**9**)[b]	yield (%)[c]
1	(4-Me)$C_6H_4SO_2$	8.0:1	75
2[d]	(4-Me)$C_6H_4SO_2$	8.1:1	81
3	$MeSO_2$	6.5:1	81
4	2-$PySO_2$	11:1	66
5	C_6H_5CO	>25:1	65
6	(4-O_2N)C_6H_4CO	>25:1	80
7	(4-Me)C_6H_4CO	>25:1	65
8	$(PhO)_2PO$	>25:1	69
9	$PhCH_2OCO$	>25:1	74
10	$PhCH_2$		<5

[a] Azide (0.24 mmol) and **7** (0.2 mmol) in THF (2.0 mL). [b] ^1H NMR ratio of crude mixture. [c] Combined yield. [d] Et_3N (1.2 equiv) was used.

benzoyl azides, irrespective of the electronic nature of the substituents (entries 5−7). Additionally, phosphoryl- and benzyloxycarbonyl azide could be also employed as reacting counterparts (entries 8−9).[8] However, relatively electron-rich azides such as alkyl or aryl variants did not react (entry 10).

On the basis of the product distribution and precedents that electron-deficient azides react with activated olefins including enamines,[9] a plausible pathway for the present reaction is depicted in Scheme 1. The transformation is assumed to be initiated by the intrahydroamination by the assistance of a metal catalyst.[10] While the emerging enamine exists as an isomeric mixture,[11] the more stable *exo*-methylene pyrrolidine adduct (**10**) is preferentially cyclized with azides giving a spiro triazoline (**11**), which is then rearranged to cycloamidine **3** upon release of diazomethane. In fact, we were able to capture in situ CH_2N_2 from a reaction in the presence of 4-phenylbenzoic acid.[12]

In the case of 1,5-aminoalkynes, *endo*-adduct **12** rather than its *exo*-isomer reacts more readily with azides.[11] Rearrangement of the resultant triazoline (**14**) is postulated to lead to **8a** upon the migration of a Me group and release of N_2.[13] It is noteworthy that the present reactions include a mild intramolecular hydroamination as the most probable key pathway, which normally takes place under much harsher conditions using late transition metal catalysts.[14]



The mechanistic interpretation gains credence by several experiments in addition to the product distribution and capture of released CH_2N_2. First, treatment of TsN_3 with an independently prepared cyclic enamines from 1-benzyl-2-pyrrolidinone using Tebbe reagent

10.1021/ja064788i CCC: $33.50

Scheme 1

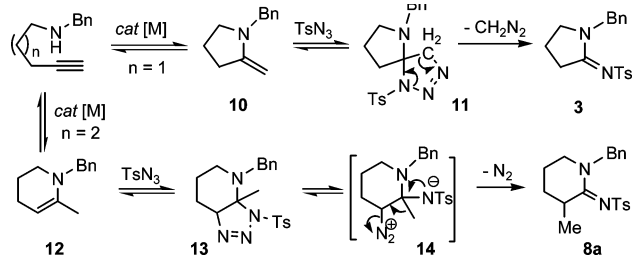
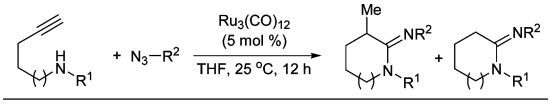
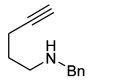
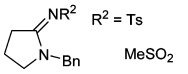
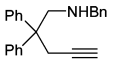
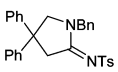
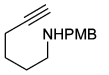
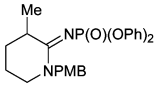
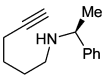
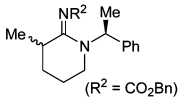
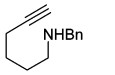
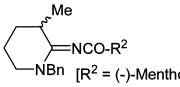
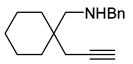
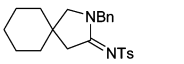
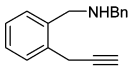
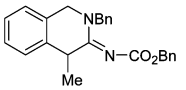


Table 2. Ru-Catalyzed Synthesis of Cyclic Amidines[a]



entry	aminoalkyne	major product	yield (%)[b]
1		 R2 = Ts	86 (4.0:1)[c]
2		MeSO2	71 (6.5:1)
3		2-PySO2	66 (10:1)
4			61 (>25:1)[c]
5[d]			80 (>25:1)
6		 (R2 = CO2Bn)	61 (>25:1)[e]
7		 [R2 = (-)-Menthol]	71 (>25:1)[f]
8			63 (3.6:1)
9			83 (>25:1)

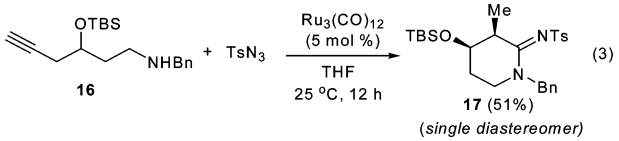
[a] Azide (0.24 mmol) and aminoalkyne (0.2 mmol) in THF (2.0 mL). [b] Isolated yields and NMR ratio of major/minor. [c] Et_3N (1.2 equiv) was used. [d] PMB: *p*-methoxybenzyl. [e] A 1.6:1 mixture of the syn and anti diastereomers. [f] Mixture of two diastereomers (1.2:1).

provided a mixture of cyclic amidines (the same products as in entry 1 of Table 2) with a ratio of 2.7:1.[6] Second, when a *d*-labeled aminoalkyne (**7**-d_2) was allowed to react with an azide, the *d*-incorporation was observed at both the migrated Me and methinyl proton in the main product (**15**, eq 2), suggesting a pathway for the 1,3-hydrogen (deuterium) shift into the secondary α-carbon relative to the imino group.

A wide range of aminoalkynes was readily reacted with electron-deficient azides by virtue of $Ru_3(CO)_{12}$ catalyst leading to cyclic amidines with high efficiency (Table 2). When 1,4-aminoalkynes were employed, 5-ring amidines devoid of a Me group at the α-position were obtained as major products, and derivatives bearing an α-methyl were generated as minor (entries 1−4 and 8). The ratio varies depending on the type of aminoalkynes and azides. By contrast, reaction of 1,5-aminoalkynes with azides provide six-ring amidines having a Me group on the ring as major products.

Readily removable functional groups at the *N*-amino or imino position could be installed in good yield (entry 5). When a substrate having an optically active amino group was employed, the resulting cycloamidine was obtained with modest diastereoselectivity (entry 6). Additionally, no significant stereo induction was observed when a chiral azide was employed (entry 7). However, it should be mentioned that the present one-pot reaction readily delivers molecular complexity such as spirocyclic amidine or bicyclic tetrahydroisoquinoline system (entries 8−9).

In the case of aminoalkyne **16** having a resident in the backbone, 3,4-*syn*-cycloamidine **17** was obtained as the sole product (eq 3). Hence, the Me-group migration step proceeded with a perfect diastereoselectivity.



In conclusion, we have developed a new synthetic methodology by bridging two reactions in a tandem manner. It demonstrates, as the proof-of-principle, that equilibria tandem sequence can be favorably driven by an irreversible step, thereby enabling a facile one-pot synthetic route to deliver molecular complexity under unprecedented mild conditions. It is anticipated that applications of this concept would pave a new way to synthetically valuable processes without relying on the traditional linear approaches.

Acknowledgment. Dedicated to Professor Sunggak Kim on the occasion of his 60th birthday. This research was supported by KRF Grant KRF-2005-015-C00248 and by the CMDS at KAIST.

Supporting Information Available: Data of ^1H and ^{13}C NMR spectra of new compounds, and two CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) For details, see Supporting Information.

(7) *N*-Propyl substrate afforded a similar result compared to *N*-benzyl.

(8) No reaction was observed using internal aminoalkynes with azides.

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JA064788I