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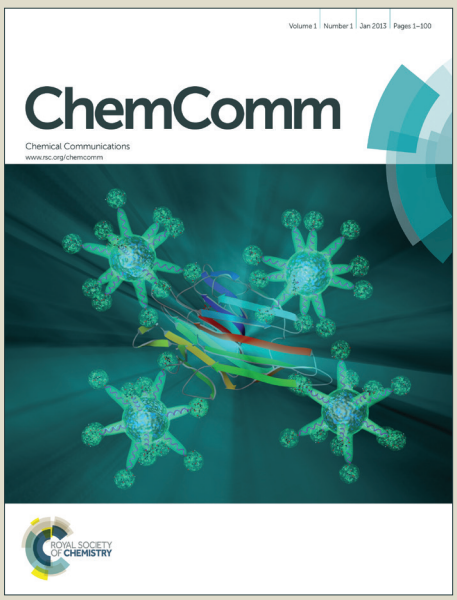

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ARTICLE TYPE

A base-catalyzed cycloisomerization of 5-cyano-pentyne derivatives: efficient synthesis of 3-cyano-4,5-dihydro-1*H*-pyrroles

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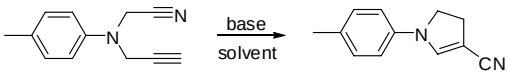
A base-catalyzed cycloisomerization of 5-cyano-pentyne bearing a terminal alkyne group has been developed under metal-free conditions. This reaction involves a tandem process providing an efficient access to 3-cyano-4,5-dihydro-1*H*-pyrroles in good to excellent yield in an atom-economic manner with 1,3-cyano migration as the key transformation.

Nitriles are an important class of organic compounds and have been used as pharmaceuticals, agrochemicals, and optoelectronic materials.[1] They also serve as versatile synthetic scaffolds to a diverse array of building blocks such as aldehydes, ketones, amides, carboxylic acids, and amines.[1] Accordingly, the development of novel and efficient synthetic methods for nitriles has been a major topic in synthetic organic chemistry.[2-6] In this area, the most straightforward and atom economical process should be the carbocyanation reaction, which allows introduction of cyano and/or an another organic group simultaneously toward unsaturated carbon-carbon bonds through direct cleavage of a C–CN bond without generating waste.[3-6] In the past several decades, two strategies for the carbocyanation reaction of alkynes have been developed: 1) the transition-metal-catalyzed carbocyanation reaction of alkynes[3,5]; 2) the free-radical-induced carbocyanation reaction of alkynes under UV-light irradiation or in the presence of azobisisobutyronitrile (AIBN).[6] Obviously, the development of novel methods for the carbocyanation reaction of alkynes is of great significant and remains a challenge. Herein, we wish to report a base-catalyzed cycloisomerization of 5-cyano-pentyne derivatives, which undergoes a tandem process involving a 1,3-cyano migration to give 3-cyano-4,5-dihydro-1*H*-pyrroles in good to excellent yield.

Domino reactions are attractive to industry and research laboratories because of their potential to save solvents, reagents, time and energy.[7] During our research on syntheses of heterocyclic[8,9] and carbocyclic compounds[10] by domino reactions, some useful methods have been demonstrated starting from functionalized alkynes.[9,10d] Very recently, several routes were also developed for the synthesis of furo[3,2-*b*]-β-lactams[11a], furo[3,2-*b*]-γ-lactams[11a] and pyrroles[11b,c] starting from propargylamine derivatives. Encouraged by the these results,[8-11] together with the synthetic versatility of functionalized propargylamine derivatives[12], the intramolecular cyclization reaction of propargyl amines **1** bearing cyanomethyl group on the nitrogen atom was investigated. As a result, it was found that the unprecedented intramolecular carbocyanation reaction of 5-cyano-pentyne **1a** (0.5 mmol) can easily proceed to give the 3-cyano-4,5-dihydro-1*H*-pyrrole **2a** in 92% yield in the presence of 30% NaH in DMF (2.0 mL) at 130 °C for 7 h (Table 1, entry 1).[13] Further decreasing the amount of NaH and the temperature of reaction led to lower yields of **2a** (Table 1, entries 2-4). Other bases, such as NaOH, K_2CO_3 and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), were less (Table 1, entries 5 and 6) or not effective (Table 1, entry 7). In comparison to other solvents such as DMSO, CH_3CN and THF (Table 1, entries 8-10), DMF has proved to be the best choice.

Table 1 Optimization of reaction conditions



1a **2a**

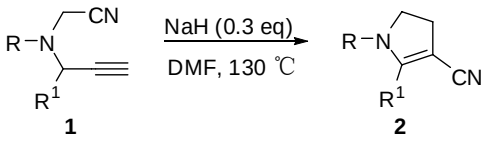
Entry	Base (equiv.)	Solvent	T (^{0}C)	t/h	Yield (%)[b]
1	***NaH (0.3)***	***DMF***	***130***	***7.0***	***92***
2	NaH (0.2)	DMF	130	7.0	85
3	NaH (0.3)	DMF	120	7.0	36
4	NaH (0.3)	DMF	110	7.0	14[c]
5	NaOH (0.3)	DMF	130	7.0	25
6	K_2CO_3 (0.3)	DMF	130	7.0	19
7	DBU (0.3)	DMF	130	7.0	--
8	NaH (0.3)	DMSO	130	7.0	62
9	NaH (0.3)	toluene	reflux	24	--
10	NaH (0.3)	THF	reflux	24	--

[b] Isolated yield. [c] Substrate **1a** was recovered in 61% yield.

Under optimal conditions (Table 1, entry 1), the scope of the base-catalyzed intramolecular carbocyanation reaction of 5-cyano-pentynes **1** was studied and the results are summarized in Table 2. It is obvious that the tandem reaction showed broad tolerance for various R substituents of **1**. All selected substrates **1a-n**, bearing phenyl (entry 2), electron-rich (entries 1 and 3-6), electron-deficient (entries 7 and 8) aryl, 2-naphthyl (entry 9), benzyl (with either an electron-donating or electron-withdrawing group on the benzene ring, entries 10-12) and alkyl R groups (entries 13 and 14) on the nitrogen atom, could efficiently undergo the intramolecular carbocyanation reaction to give the corresponding 3-cyano-4,5-dihydro-1*H*-pyrroles **2a-n** in high to excellent yields. More importantly, even in the case of the

substrate **1o** with a methyl group (R^1 = Me), the domino reaction also worked well, yielding the desired product **2o** in 68% yield (entry 15).

Table 2 NaH-Catalyzed intramolecular carbocyanation reaction of alkynes **1**[a]



1 **2**

Entry	1	R	R^1	t/h	2	Yield (%)[b]
1	**1a**	4-MeC_6H_4	H	7	**2a**	92
2	**1b**	C_6H_5	H	8	**2b**	80
3	**1c**	3-MeC_6H_4	H	8	**2c**	80
4	**1d**	2-MeC_6H_4	H	10	**2d**	77
5	**1e**	3,5- MeC_6H_3	H	8	**2e**	85
6	**1f**	4-MeOC_6H_4	H	10	**2f**	92
7	**1g**	4-FC_6H_4	H	8	**2g**	81
8	**1h**	4-ClC_6H_4	H	9	**2h**	83
9[c]	**1i**	2-Naphth	H	7	**2i**	90
10	**1j**	$C_6H_5CH_2$	H	5	**2j**	95
11	**1k**	4-Me$C_6H_4CH_2$	H	5	**2k**	88
12	**1l**	4-Cl$C_6H_4CH_2$	H	5	**2l**	82
13	**1m**	n-Bu	H	5	**2m**	90
14	**1n**	EtO_2CCH_2	H	4	**2n**	87
15[c]	**1o**	4-MeC_6H_4	CH_3	7	**2o**	68

[a] *Reaction conditions:* **1** (0.5 mmol), NaH (0.15 mmol), DMF (2.0 mL), 130 °C, 4-10 h. [b] Isolated yield. [c] 0.6 equiv. NaH was used.

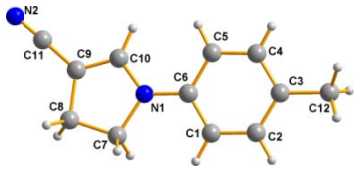
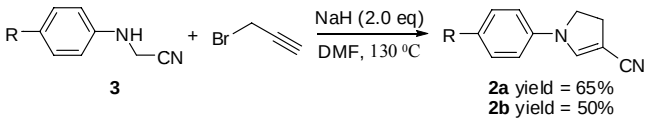


Figure 1. ORTEP drawing of **2a**.

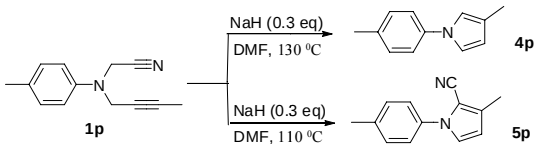
To simplify the above base-catalyzed intramolecular carbocyanation reaction, the two-component reaction combined with the in situ generation of substrates **1** under basic conditions was examined. To our delight, after optimization of the reaction conditions, it was found the two-component reaction of 2-arylaminoacetonitriles **3** with 3-bromoprop-1-yne can also proceed well in the presence of 2.0 equiv of NaH in DMF at 130 °C for 12 h to give 3-cyano-4,5-dihydro-1*H*-pyrroles **2a** and **2b** in 65% and 50% yields (along with some complex mixtures), respectively (Scheme 1).



3

Scheme 1 One-pot reaction.

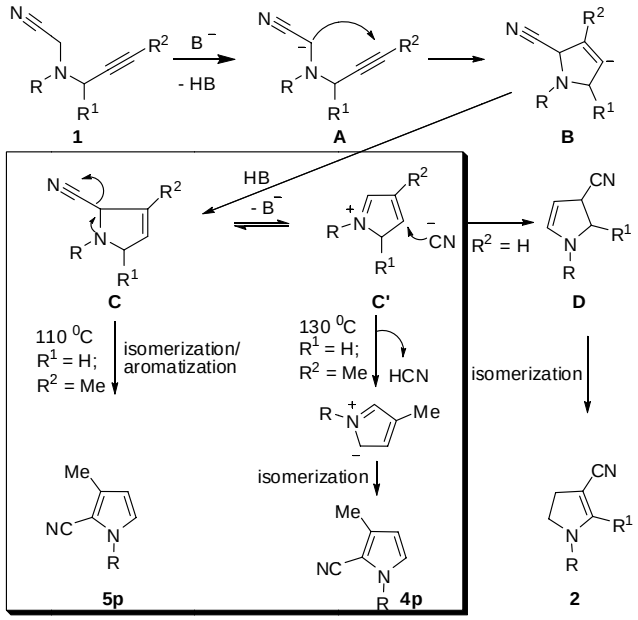
In order to investigate the influence of substituted group at the terminal carbon of alkyne triple bond of **1** on the reaction, the reaction of **1p** was examined. As a result, under essentially the identical conditions as above, the cyclization-decyanation product **4p** was produced in 86% yield (Scheme 2). When the reaction was performed at 110 °C for 10 h, 3-methyl-2-cyano-1-*p*-tolyl-1*H*-pyrrole **5p** was produced in 70% yield along with 10% of **4p**.



1p

Scheme 2 NaH-Catalyzed intramolecular cyclization reaction of **1p**.

On the basis of the above experimental results together with the related reports,[11,12,14,15] a possible mechanism was proposed (Scheme 3). Initially, in the presence of NaH, the cyano-stabilized carbon anion intermediate **A**, generated via the deprotonation of carbon atom adjacent to CN group of **1**, undergoes an intramolecular cyclization in a 5-endo-dig fashion to give intermediate **B**.[14] Protonation of **B** leads to the formation of key intermediates **C** and **C'** in equilibrium in which **C'** is formed through the attack by the lone electron pair of amine nitrogen atom with cyano group behaves as the leaving group (a retro-Strecker process).[15] Therefore, pyrrole product **5p** will be formed via intermediate **C** through a isomerization/aromatization sequence in the presence of base under aerobic atmosphere.[16] At higher temperature than the formation of **5p**, the formation of pyrrole **4p** is to be proffered via intermediate **C'** through elimination of HCN followed by isomerization (Scheme 3).



Scheme 3 Proposed mechanism.

On the other hand, the reactions of 5-cyano-pentynes **1a-o** bearing a terminal alkyne group, the attack of the cyanide anion of **C'** on the carbon atom adjacent to R^1 would be preferred, which leads to intermediate **D** and then isomerizes to 3-cyano-4,5-dihydro-1*H*-pyrroles **2** in the presence of base (Scheme 3).

In conclusion, we have developed a base-catalyzed cycloisomerization of 5-cyano-pentyne derivatives. This reaction involves a novel 1,3-cyano migration to provide a highly facile

and efficient access to various 3-cyano-4,5-dihydro-1*H*-pyrroles in good to excellent yields in an atom-economic manner from the readily available starting materials. Further studies are in progress.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of data for all new compounds. CCDC 994058 (**2a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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13 Crystal data for **2a**: $C_{12}H_{12}N_2$, white crystal, M = 184.24, Monoclinic, P2(1)/c, a = 7,7787(10) Å, b = 8.3955(11) Å, c = 15.691(2) Å, α = 90.00 °, β = 93.859(2) °, γ = 90.00 °, V = 1022.4(2) Å^3, Z = 4, T = 293(2), F_{000} = 392, R_1 = 0.0523 , wR_2 = 0.1252. CCDC 994058. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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