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Base-Mediated Direct Transformation of *N*-Propargylamines into 2,3,5-Trisubstituted 1*H*-Pyrroles

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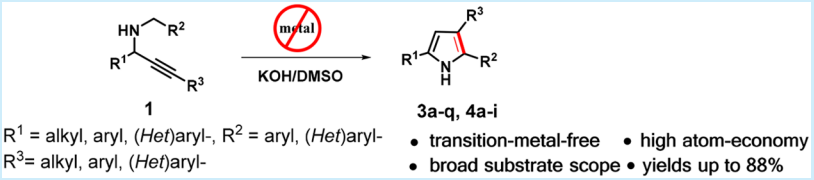
Supporting Information



ABSTRACT: An efficient and base-mediated intramolecular cyclization of *N*-propargylamines for the synthesis of structurally diversified pyrroles in high yield has been described. The developed methodology is broadly applicable and is tolerated by a variety of functional groups. Key intermediates of natural product discoipyrrole C as well as HMG-CoA-reductase inhibitor have been successfully synthesized using developed chemistry. The proposed mechanism was supported by control experiments.

Pyrroles are ubiquitous heterocyclic motifs present in various natural products and a wide range of pharmaceutically active molecules (Figure 1).[1,2] In addition, pyrrole core having templates also exhibit anti-tumor, anti-HIV, and anti-hyperglycemic activities.[3] Furthermore, they are broadly used in materials chemistry.[4]

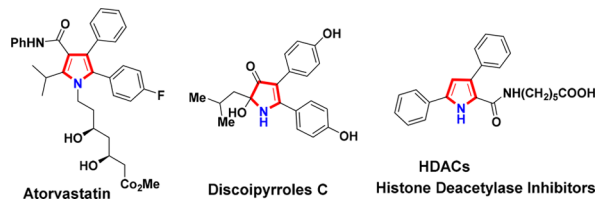
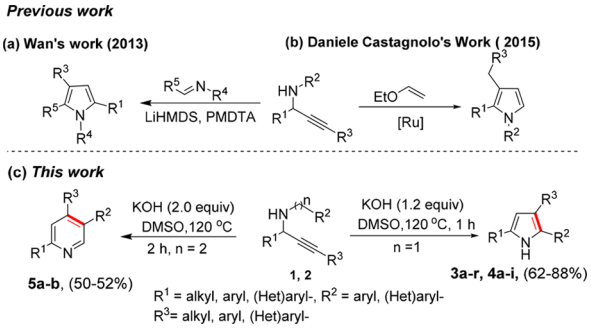


Figure 1. Representative biologically active pyrrole scaffolds.

Several traditional syntheses of the pyrroles in the literature was reported as Paal−Knorr[5a,b] and Hantzsch[6] reactions. In the past decades, several methods have been documented for the synthesis of pyrroles such as metal-catalyzed reactions,[7] multicomponent reactions,[8] and base-catalyzed reactions.[9] However, the use of expensive metal catalysts, prolonged reaction time, and limited substrate scope restricted their application for industrial purposes. Thus, the development of sustainable and transition-metal-free approaches for the synthesis of multisubstituted pyrroles is of vital importance.

N-Propargylamines are key precursors for the construction of various heterocyclic compounds and natural products.[10] Among them, synthesis of pyrroles from *N*-proparagylamine[11] has gained significant attention in recent years. Bremner and co-worker[12] have reported the synthesis of pyrroles from *N*-propargylamines with aldehydes. In 2011, synthesis of pyrroles by a Pd(II)-catalyzed cascade reaction of *N*-propargylamines and alkynes through *5-endo-dig* cyclization was demonstrated by Trost and co-workers.[13] Later, Wan and co-workers[14] reported the synthesis of tetrasubstituted pyrroles by the reaction of *N*-propargylamines with imines (Scheme 1a). In 2015, Castagnolo's group[15] reported the synthesis of 1,2,3-trisubstituted pyrroles from propargylamines via enyne cross-metathesis using the Grubbs II catalyst (Scheme 1b). More recently, Shen's group[16] has explored the synthetic utility of *N*-propargylamines for the synthesis of substituted furans through the base-catalyzed [3 + 2] cycloaddition to aldehydes. The direct transformations of *N*-propargylamines into pyrroles without a coupling partner have not been much explored. Keeping these challenges in mind and continuation of our ongoing research on base-mediated reactions[17] and *N*-heterocyclic synthesis,[18] herein, we have demonstrated a base-mediated direct transformation of *N*-propargylamine into 2,3,5-trisubstituted 1*H*-pyrroles under transition-metal-free conditions (Scheme 1c).

Scheme 1. Novel Approaches to Synthesis of Pyrroles



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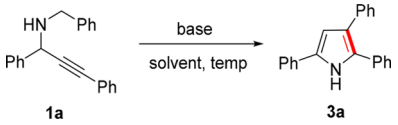
We have initiated our investigation with *N*-benzyl-1,3-diphenylprop-2-yn-1-amine **1a** as our model substrate. The reaction of **1a** with potassium hydroxide (1.2 equiv) in DMSO at 25 °C only led to none or a trace amount of pyrrole **3a** (Table 1, entry 1). The increase in temperature of the reaction improved the yield of the product **3a** (entries 2 and 3). The product **3a** was obtained in 75% yield at 120 °C (entry 4). The results of entries 2−4 clearly suggest that temperature has a significant role in the reaction. The catalytic amount of base was found to be inefficient for the formation of pyrrole **3a** (entry 5). No significant change in the yield of the product **3a** was observed on performing the reaction of **1a** under an inert atmosphere (entry 6). On switching to polar solvents such as DMF, NMP or DMA could not improve the yield of the desired product **3a** (entries 7−9). The desired product was not formed when the reaction was performed in toluene as solvent (entry 10). Other bases such as CsOH, NaOH, LiOH, K^{t}OBu, K_3PO_4, and DBU were found inferior for the reaction (entries 11−16), whereas DABCO, K_2CO_3, and Cs_2CO_3 failed to provide the desired product (entries 17−19). In the absence of a base, no product was formed (entry 20).

Table 1. Optimization of Reaction Conditions[a,b]



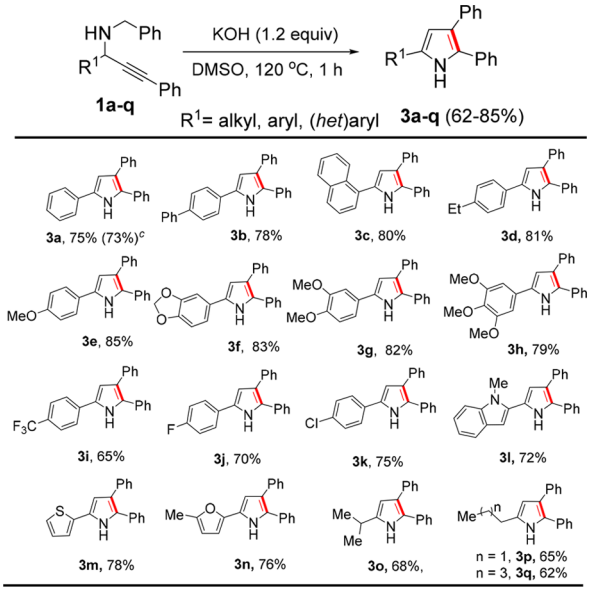
1a **3a**

entry	base	solvent	*t* (h)	temp (°C)	yield of **3a**[b] (%)
1	KOH	DMSO	12	25	trace
2	KOH	DMSO	12	60	50
3	KOH	DMSO	12	80	65
4	KOH	DMSO	1	120	75
5	KOH[c]	DMSO	1	120	25
6	KOH[d]	DMSO	1	120	74
7	KOH	DMF	1	120	25
8	KOH	NMP	1	120	30
9	KOH	DMA	1	120	20
10	KOH	toluene	1	120	n.r.
11	CsOH	DMSO	1	120	53
12	NaOH	DMSO	1	120	45
13	LiOH	DMSO	1	120	30
14	K^{t}OBu	DMSO	1	120	20
15	K_3PO_4	DMSO	1	120	55
16	DBU	DMSO	2	120	35
17	DABCO	DMSO	8	120	n.r.
18	K_2CO_3	DMSO	12	120	n.r.
19	Cs_2CO_3	DMSO	12	120	n.r.
20		DMSO	2	120	n.r.

[a]Reactions were performed using 0.5 mmol of **1a** and base (1.2 equiv) in 2.0 mL of solvent. [b]Isolated yield. [c]KOH (20 mol %). [d]Under N_2 atmosphere. n.r. = no reaction. DMSO = dimethyl sulfoxide, DMF = dimethylformamide, DMA = dimethylacetamide.

Under the optimized conditions, we explored the scope of the base-mediated transformation of various substituted *N*-propargylamines to pyrroles (Scheme 2). The reaction was first explored by the variation of R^1 on the *N*-propargylamine **1**. The substrate **1a−d** having electronically neutral aryl groups (such as Ph, biphenyl, naphthyl, and 4-ethylphenyl) as an R^1 gave the cyclized products **3a−d** in 75−81% yields. Substrates **1e−h** with electron-rich substituents as R^1 group provided 2,3,5-trisubstituted pyrroles **3e−h** in good to excellent yields (79−85%).

Scheme 2. Scope of Aryl/Heteroaryl/Alkyl Aldehydes[a,b]

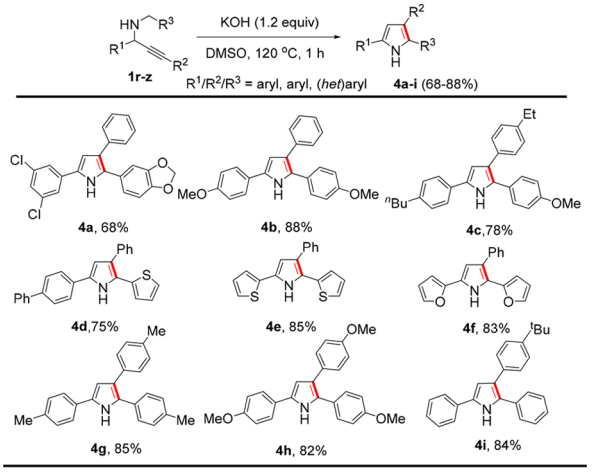


[a]Reactions were performed using 0.5 mmol of **1a−q** and KOH (1.2 equiv) in 2.0 mL of DMSO. [b]Isolated yield. [c]Using 1.0 mmol of **1a**.

The substrates **1i** and **1j** having trifluoromethyl (−CF_3) and fluoro (−F) groups at the para position afforded the corresponding pyrroles **3i** and **3j** in 65−70% yields. Halogenated substrate **1k** was well tolerated to afford the cyclized product **3k** in 75% yield. Substrates **1l−n** bearing a heterocyclic substituent as an R^1 group such as 2-indolyl (**1l**), 2-thienyl (**1m**), and 2-furyl (**1n**) provided the desired products **3l−n** in 72−78% yields. Notably, when unactivated *N*-proparagylamines **1o−q** were employed as the substrate, pyrroles **3o−q** were obtained in good yields.

In order to gain insight into the above results (Scheme 2), we explored differently substituted R^1, R^2, and R^3 in the *N*-propargylamine moiety (Scheme 3). The propargylamine **1r** with the electron-withdrawing group (R^1) and an electron-releasing group (R^2) provided the pyrrole **4a** in 68% yield. The

Scheme 3. Scope of Aryl/Heteroaryl/Alkyl-Substituted Pyrroles



[a]Reactions were performed using 0.5 mmol of **1r−z** and KOH (1.2 equiv) in 2.0 mL of DMSO. [b]Isolated yield.

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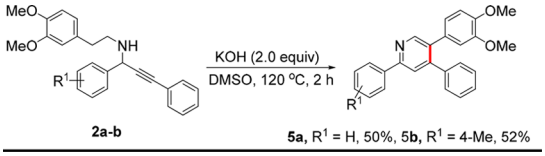
electron-rich propargylamine substrates **1s** (R^1 and R^2 = *p*-OMe−C_6H_4) and **1t** (R^1 = *p*-Bu−C_6H_4 and R^2 = *p*-OMe−C_6H_4) are viable substrates and gave the desired products **4b** and **4c** in 78 and 88% yields, respectively. Substrate **1u** also underwent the desired reaction to gave the desired product **4d** in good yield. Interestingly, 3-phenyl-2,5-di(thiophen-2-yl)-1*H*-pyrrole **4e** and 3-phenyl-2,5-di(furan-2-yl)-1*H*-pyrrole **4f** were obtained in 85 and 83% yields, respectively, when R^1 and R^2 were heterocyclic groups such as thiophene (**1v**) and furan (**1w**). The synthesis of 2,3,5-trisubstituted (−NH) pyrroles having an identical substituent such as $R^1 = R^2 = R^3$ = *p*-Me−C_6H_4 (**4g**) and $R^1 = R^2 = R^3$ = *p*-OMe−C_6H_4 (**4h**) were attained successfully under the standard reaction conditions. The bulky *tert*-butyl substituent at the para position of alkyne (R^3) was successful in providing the desired product **4i** in 84% yield.

The scope of this reaction was further extended toward the synthesis of 2,4,5-trisubstituted pyridines, utilizing substrate **1** having R^3 as arylethylamine (Scheme 4). The reaction of *N*-(3,4-dimethoxyphenethyl)-1,3-diphenyl prop-2-yn-1-amine **2a** in the presence of the strongly basic KOH−DMSO system provided the desired product **5a** in 50% yield. The substrates **2b** with the electron-releasing group effectively provided the cyclized product **5b** in moderate yield (Scheme 4, see the Supporting Information).

Scheme 4. Synthesis of 2,4,5-Trisubstituted Pyridines[a,b]

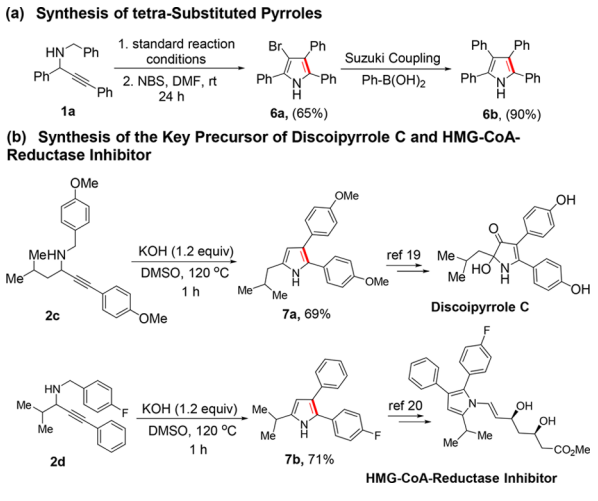


[a]Reactions were performed using 0.5 mmol of **1aa−bb** and KOH (2.0 equiv) in 2.0 mL of DMSO. [b]Isolated yield.

To demonstrate the synthetic utility of the reaction's products, 2,3,5-triaryl-1*H*-pyrrole **3a** was easily converted to the bromo-substituted pyrroles **6a** in 65% yield which on Suzuki coupling reaction provided tetraphenyl-1*H*-pyrrole **6b** in 90% yield (Scheme 5a).

To illustrate the application of our developed chemistry, the key intermediate **7a** of natural product discoipyrrole C and **7b** of HMG-CoA-reductase inhibitor were obtained in good yields.

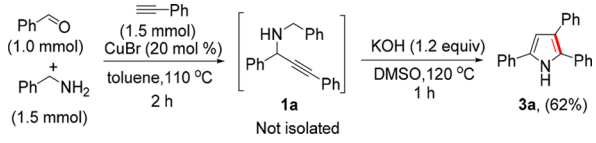
Scheme 5. Synthetic Application



The developed strategy provides a simple synthetic route with short reaction time and good yield compared with other reported protocols for the synthesis of these key intermediates (Scheme 5b).[19,20]

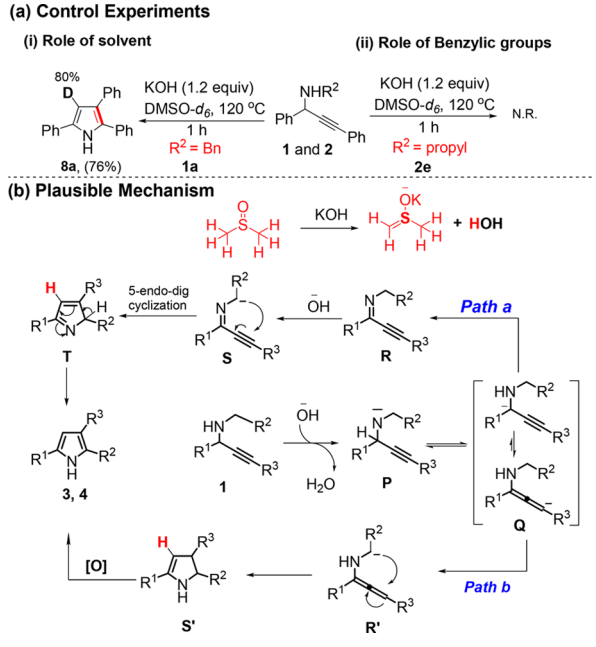
Finally, a one-pot, sequential A^3 coupling of aldehyde, amine, and alkyne using CuBr/toluene as a catalyst has been utilized to generate the *N*-propargylamine[22] **1a**, which further underwent cyclization in the presence of KOH−DMSO at 120 °C to provide 2,3,5-trisubstituted (NH) pyrroles **3a** in moderate yield (Scheme 6). The one-pot methodology of the synthesized heterocycles is likely to be of high synthetic utility.

Scheme 6. Sequential One-Pot Synthesis of 3a



To gain insight into the mechanism, we have performed two sets of control experiments: (i) to find the role of solvent and (ii) to find the role of the benzylamine group. When we performed the reaction of **1a** in KOH−DMSO-d_6, 80% deuterium incorporation in the desired product **8a** was observed. This result suggests that the incoming proton originates from solvent (Scheme 7a, i). Further, to ascertain the role of a benzyl group, the reaction of **1ac** with a propyl group was carried out under standard reaction conditions which did not furnish the desired product (Scheme 7a, ii). This observation suggests that the presence of a benzylic substituent R^2 is necessary for the reaction.

Scheme 7



On the basis of the previous reports[13,17,21] and with the support of control experiments (Scheme 7b), we have proposed a plausible mechanism for the formation of 2,3,5-trisubstituted pyrroles. The mechanism is initiated by the base-assisted deprotonation of *N*-propargylamine **1**, forming a species **P** which undergoes allene formation to **Q**. From **Q**, two possible

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mechanistic pathways have been proposed. In *path a*, species **Q** undergoes a hydride abstraction of a two-electron oxidation/deprotonation to generate enyne **R**,[21c] which further converted into anionic species **S** in the presence of a base. Subsequently, species **S** undergoes 5-*endo-dig* cyclization[13] to afford **T** which upon isomerization leads to the formation of pyrroles **3** and **4**. However, in *path b*, base abstracts the proton from **Q** to develop species **R′**, which undergoes intramolecular cyclization to provide 2,3-dihydro-pyrrole **S′**. The autoxidation of species **S′** afforded the desired products **3** and **4** (Scheme 7b).

In conclusion, we have described a transition-metal-, ligand-, and additive-free, base-promoted synthesis of structurally diversified 2,3,5-trisubstituted 1*H*-pyrroles from *N*-propargylamines in good to excellent yields. The reaction is atom-economical as well as environment-friendly. The developed chemistry is also successful for the synthesis of functionalized pyridines. The synthetic utility of this reaction could be extended further for the synthesis of key intermediates in natural products. The deuterium labeling experiments support the proposed mechanistic pathway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03112.

Data and spectral copies of ^{1}H and ^{13}C NMR and HRMS for target compounds (PDF)

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Notes

The authors declare no competing financial interest.

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