OL Organic Letters

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One-Pot Synthesis of N−H-Free Pyrroles from Aldehydes and Alkynes

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Cite This: *Org. Lett.* 2021, 23, 4348−4352 Read Online

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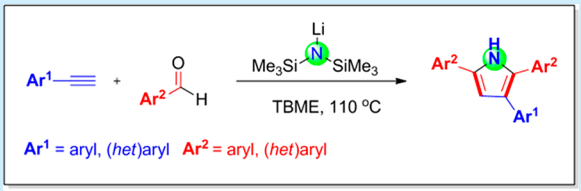
ABSTRACT: The first base-mediated intermolecular cyclization of arylaldehydes and terminal arylacetylenes for the synthesis of a wide range of pyrroles in a single step has been described. The developed methodology used commercially available starting materials and tolerated a broad range of functional groups affording 2,3,5-triaryl-substituted-1*H*-pyrroles with good yields (up to 92% yield) under mild conditions. The possible mechanism was also discussed.

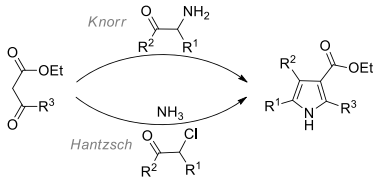


- *commercially available starting materials*
- *broad substrate scope (33 examples)*
- *yield up to 92%*

Pyrroles, among the most prevalent five-membered heterocyclic motifs, are present in a plethora of natural products,[1] and as core substructures of pharmaceuticals, also possess various bioactivities such as antifungal, antiviral, antihyperlipidemic, and anticancer activities.[2] In addition, they are also broadly applied in agrochemicals and functional materials.[3]

Accordingly, traditional routes to access pyrroles include the Knorr[4] and Hantzsch[5] reactions (Scheme 1). A majority of contemporary pyrrole synthesis involve transition-metal catalyzed pyrrole functionalization reactions (transition-metals involved),[6] multicomponent reactions,[7] and many others.[8] Recent progress along these lines has been remarkable, but highly functionalized starting materials or preformed intermediates are needed. Also, the stringent requirements for trace metal contamination in bioactive compounds, however, have driven the desire to develop transition-metal-free processes. Consequently, the demand for efficient, straightforward, and economical pyrrole synthesis from abundant feedstocks in the absence of transition metals remains high.

Scheme 1. Traditional Routes to Access Pyrroles



We are interested in silylamide base $MN(SiMe_3)_2$ (M = Li, Na, K, Cs)-mediated/catalyzed deprotonative addition reactions with substrates possessing a weakly acidic $C(sp^3)$−H bond. Recently, we developed a novel, efficient, and chemoselective method for one-pot aminobenzylation of aldehydes with toluenes based on tandem C−N and C−C bond formations (Scheme 2a).[9] More recently, this transformation has been achieved with a catalytic base.[10] Further adaptation of this strategy has led to a diverse array of routes to functionalized heterocycles, such as 2-arylindoles,[11] 2-azaarylterahydroquinolines,[12] and others.[13] The key findings include the following: (1) The Group I main group cation−π interactions facilitate toluene deprotonation. (2) $MN(SiMe_3)_2$ (M = Li, Na, K, Cs) plays two roles: one is direct deprotonation of weakly acidic $C(sp^3)$−H bonds, and the other is condensation with benzaldehyde to *in situ* generate *N*-(trimethylsilyl)imines. (3) The products are of great importance motifs. When we explored $MN(SiMe_3)_2$ (M = Li, Na, K, Cs)-*catalyzed* addition of phenylacetylene to in situ generated TMS-imines, we detected formation of trace amount of pyrrole without forming propargylamine. Herein, we present the first straightforward and practical one-pot synthesis of 2,3,5-trisubstituted pyrroles from simple feedstocks, i.e., aldehydes and terminal alkynes (Scheme 2b). Compared with previous strategies by Wan, Verma, and Cui,[14] our method provides a valuable alternative to synthesis of N−H pyrroles, circumventing the need for preformed imines, propargylamines, or functionalized ynones (Scheme 2c−e). Also, these N−H-free pyrroles provide a handle to generate a diverse array of N-protected pyrrole derivatives.

Received: April 14, 2021
Published: May 20, 2021

https://doi.org/10.1021/acs.orglett.1c01287
Org. Lett. 2021, 23, 4348−4352

Scheme 2. Base-Mediated Deprotonative Functionalization and Base-Mediated Routes to Access Pyrroles

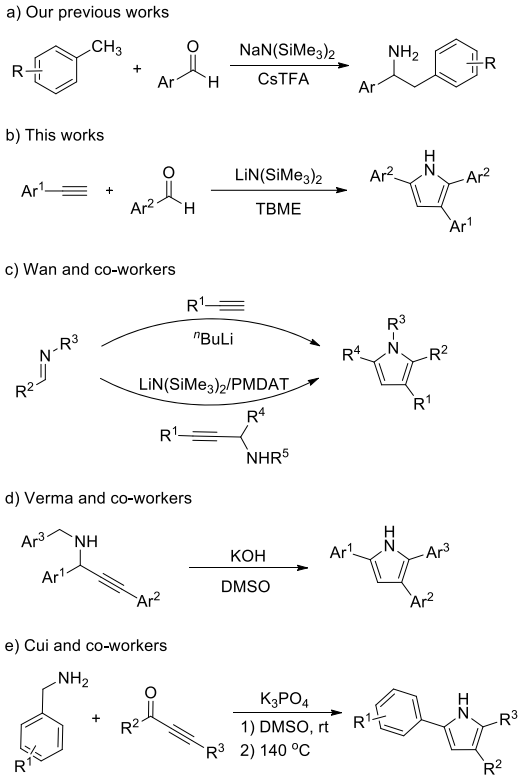
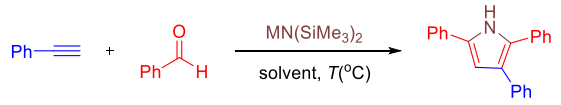


Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	base	1a:2a:base	solvent	T(°C)	AY[b] (%)
1	$KN(SiMe_3)_2$	1:1:3	CPME	110	18
2	$NaN(SiMe_3)_2$	1:1:3	CPME	110	10
3	$LiN(SiMe_3)_2$	1:1:3	CPME	110	24
4	$LiN(SiMe_3)_2$	1:2:4	CPME	110	43
5	$LiN(SiMe_3)_2$	1:2:4	DME	110	16
6	$LiN(SiMe_3)_2$	1:2:4	THF	110	0
7	$LiN(SiMe_3)_2$	1:2:4	i-Pr_2O	110	35
8	$LiN(SiMe_3)_2$	1:2:4	dioxane	110	28
9	$LiN(SiMe_3)_2$	1:2:4	PhMe	110	41
10	$LiN(SiMe_3)_2$	1:2:4	TBME	110	47
11	$LiN(SiMe_3)_2$	1:2:4	TBME	100	44
12	$LiN(SiMe_3)_2$	1:2:4	TBME	80	<5
13[c]	$LiN(SiMe_3)_2$	1:2:4	TBME	110	64[e]
14[d]	$LiN(SiMe_3)_2$	1:2:4	TBME	110	63[e]
15[c]	$LiN(SiMe_3)_2$	1:2:3	TBME	110	84[e]
16[c]	$LiN(SiMe_3)_2$	1:3:4	TBME	110	75[e]

[a]Reactions were performed on a 0.1 mmol scale in 1 mL of solvent (0.1 M) for 12 h. [b]Assay yields of **3a** were determined by HPLC analysis. [c]Reactions were performed in 0.5 mL of solvent (0.2 M). [d]Reactions were performed in 0.2 mL of solvent (0.5 M). [e]Isolated yield. CPME = cyclpentyl methyl ether, DME = ethanediol dimethyl ether, THF = tetrahydrofuran, i-Pr_2O = isopropyl ether, dioxane = 1,4-dioxane, TBME = methyl *tert*-butyl ether.

To initiate the optimization of the tandem reaction with phenylacetylene **1a** and benzaldehyde **2a**, we examined three different bases [$KN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $LiN(SiMe_3)_2$] using CPME (cyclopentyl methyl ether) as solvent at 110 °C for 12 h, affording the desired product **3a** in 24% yield with $LiN(SiMe_3)_2$ as the promising hit (entry 3) (Table 1). Increasing the amount of **2a** from 1 to 2 equiv and improving the loading of $LiN(SiMe_3)_2$ from 3 to 4 equiv led to an enhanced yield of **3a** (43%, entry 4). Additionally, other ethereal solvents (CPME vs DME, THF, $^iPr_2O$, dioxane, and TBME) and noncoordination toluene were also examined under the conditions of entry 4. The reaction in TBME exhibited the highest yield (47%, entry 10 vs entries 4−9). Further screening revealed that decreasing the reaction temperature from 110 to 100 °C had little effect on the yield of **3a** (entry 10 vs entry 11). When the reaction was performed at 80 °C, a low AY of **3a** was obtained (entry 10 vs entry 12), indicating that decreasing the temperature had a detrimental impact on the AY of **3a**. Furthermore, increasing the concentration of the reaction had little impact on the yield, as exemplified in entries 13 (0.2 M, 64% yield) and 14 (0.5 M, 63% yield). Finally, we reoptimized the ratio of substrate **2a** and the base with TBME under the conditions of entry 13 (entry 13 vs entries 15−16), which revealed significant change in the yield of the product **3a** with entry 15 having the highest yield (84%). Therefore, the optimized conditions employed 2 equiv of benzaldehyde (**2a**), 1 equiv of phenylacetylene (**1a**), and 3 equiv of $LiN(SiMe_3)_2$ in TBME (0.2 M) at 110 °C for 12 h. It should be noted that 2 equiv of $LiN(SiMe_3)_2$ was used to condense with benzaldhyde and eliminate via aza-Peterson reaction to generate *in situ* *N*-(trimethylsilyl)imines.

Under the optimized conditions, the scope of the base-mediated cyclization of phenylacetylene (**1a**) with various substituted arylaldehydes **2** was explored under the standard conditions. In general, these transformations gave the N−H-free pyrrole derivatives with moderate to good yields (Scheme 3). The aldehyde substrates with Cl, Br, and F atoms at the *para* position afforded the corresponding pyrroles (**3b**−**3d**) in 68%, 38%, and 45% yields, respectively. The low yield of **3c** was possibly due to the decomposition of *p*-bromobenzaldehyde under our reaction conditions. The halogen-containing pyrroles could be easily converted to further functionalized products via cross-coupling strategy. Aromatic aldehydes bearing electron-donating groups, such as 4-OMe, 3,4-$(OMe)_2$, and 4-SMe (**2e**−**2g**), underwent these tandem reactions and generated the desired products in 46−77% yield. Besides, aromatic aldehyde with a weak electronegative 4-OCF_3 substituent was also tolerated in the reaction condictions, furnishing product **3h** with 57% yield. Aldehydes possessing a methyl group in the *ortho*, *meta*, and *para* position furnished the desired products (**3i**−**3k**) smoothly in 62−83% yield, respectively. Moreover, aldehydes containing 3,5-di-$(CH_3)_2$ (**2l**), 4-*t*-Bu (**2m**), and 4-phenyl (**2n**) substituents reacted with phenylacetylene (**1a**) to form corresponding products in 62%, 59%, and 70% yields, respectively. Among them, product **3l** was also characterized by single X-ray diffraction. Using π-extended 1-naphthaldehyde (**2o**) and 2-naphthaldehyde (**2p**) under the standard conditions provided the desired product (**3o**, **3p**) in 58% and 77% yields, respectively. Heterocyclic compounds are present in many agrochemicals and pharmaceuticals. Substrate containing benzofuran heterocycle was also found to successfully engage in this transformation, providing the corresponding pyrrole (**3q**) in 53% yield. Besides, other substrates of aldehydes such as cinnamaldehyde, *N*-methylpyrrole-2-carboxaldehyde, and

https://doi.org/10.1021/acs.orglett.1c01287
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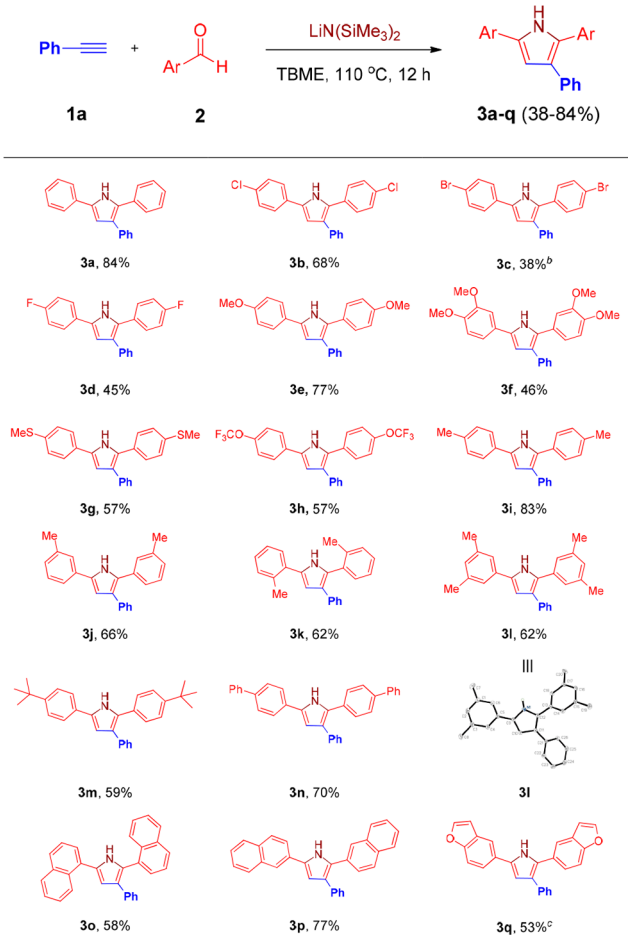
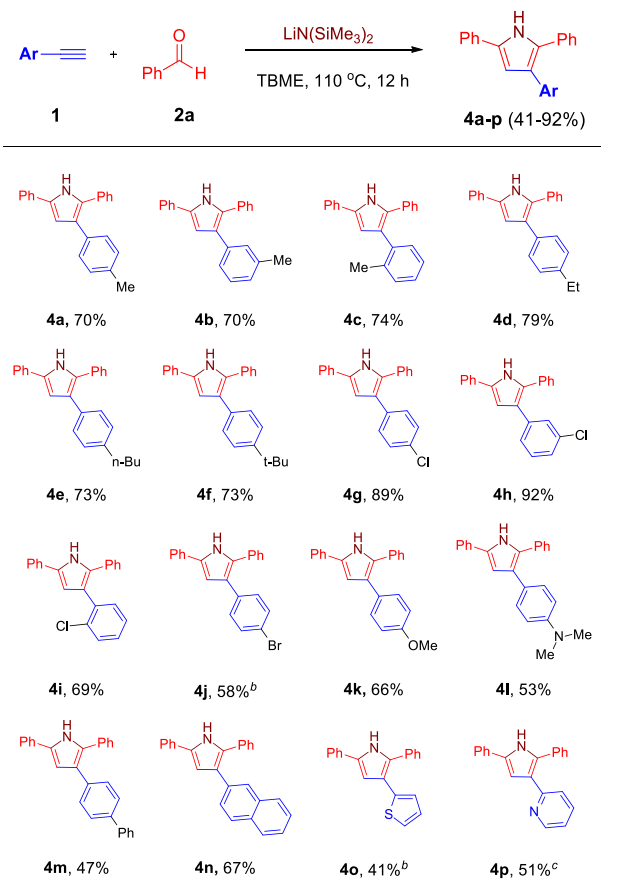
Scheme 3. Substrate Scope of Arylaldehydes[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $LiN(SiMe_3)_2$ (0.3 mmol), TBME (0.5 mL); isolated yield. [b]Reaction performed at 80 °C. [c]Reaction performed for 3 h.

Scheme 4. Substrate Scope of Terminal Arylacetylenes[a]



[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $LiN(SiMe_3)_2$ (0.3 mmol), TBME (0.5 mL); isolated yield. [b]Reaction performed at 80 °C for 3 h. [c]Reaction performed at room temperature.

thiophene-2-carboxaldehyde were also examined, but they all decomposed under our standard conditions. Finally, when pivalaldehyde was employed under our standard conditions, it provided 4,4-dimethyl-1-phenylpent-1-yn-3-ol in a 95% yield instead of the pyrrole product (see the Supporting Information for unsuccessful examples).

On the basis of the successful cyclization of phenylacetylene (**1a**) with aromatic aldehydes above, we next examined the scope of terminal arylacetylenes with benzaldehyde **2a** (Scheme 4). Phenylacetylene possessing methyl group at the *para*, *meta*, and *ortho* position (**4a**–**c**), and other alkyl groups at the 4-position, such as Et (**4d**), *n*-Bu (**4e**), and *t*-Bu (**4f**), exhibited good yields (70–79%). Besides, phenylacetylene containing halogen atom on the benzene ring, including Cl in the *para*, *meta*, and *ortho* positions, and Br in the *para* position, exhibited good to excellent reactivity, providing products **4g**–**j** in 58–92% yields upon isolation, respectively. In addition, phenylacetylene bearing electron-donating 4-OMe (**4k**) and 4-$N(Me)_2$ (**4l**) groups could furnish products in 66% and 53% yield, respectively. Phenylacetylene with extended π-systems, such as those derived from 4-biphenylacetylene (**1m**) and 2-ethynylnaphthalene (**1n**) also provided products **4m** (47%) and **4n** (67%). It is noteworthy that pyrroles with heteroaryl substituents at the 3-position could be obtained from reactions of the corresponding heterocyclic acetylenes with benzaldehyde. For example, 2-thiopheneacetylene (**1o**) and 2-pyridineacetylene (**1p**) could afford the desired products **4o** (41%) and **4p** (51%). Finally, we also performed the reaction with aliphatic terminal alkynes such as 1-cyclohexynl, cyclopropyl, *n*-Bu, but these substrates did not react with benzaldehyde under our reaction condition with most of the starting materials recovered (see the Supporting Information for unsuccessful examples).

On the basis of the previous reports,[15] we have proposed a plausible mechanism for the tandem formation of 2,3,5-triaryl-1*H*-pyrroles (Figure 1). The reaction might be assumed to start with the deprotonation of acetylene **1a** under the action of the $LiN(SiMe_3)_2$ followed by the addition of acetylenic anion **A** to the *in situ* generated *N*-(trimethylsilyl)imines **B**.[9,16] This imine is formed through the aza-Peterson olefination mechanism.[9] This addition between **A** and **B** thus gives propargylamine anion **C**. The intermediate **C** subsequently undergoes a 1,2-anion shift to afford propargyllithium reagent **D**, which is in equilibrium with the allenyllithium **E**.[17] Then allenyllithium **E** is added to another molecule of imine **B** to form the intermediate **F**, followed by intramolecular cyclization to provide the intermediate **G**. Protonation with **C** results in the intermediate **H**.[14a,18] Then the elimination of aniline from **H** gives intermediate **I**. Finally, the intermediate **I** is hydrolyzed to produce the desired pyrroles **J**.

To summarize, we have developed a novel method for the synthesis of triaryl-substituted pyrroles in one step from

https://doi.org/10.1021/acs.orglett.1c01287
Org. Lett. 2021, 23, 4348–4352

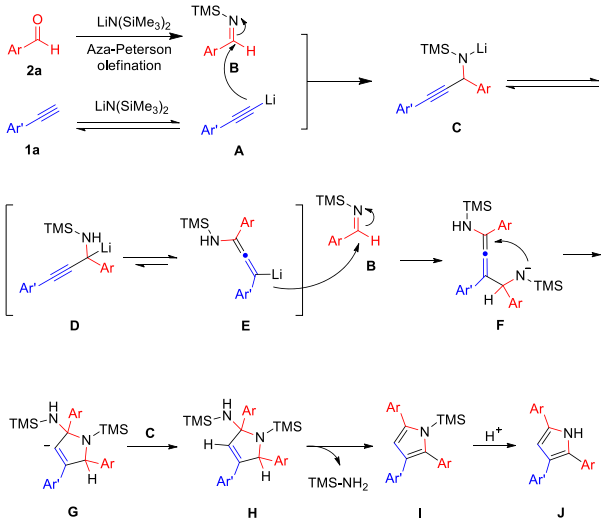


Figure 1. Possible mechanisms of pyrroles formation.

feedstocks aryl-aldehydes and terminal acetylenes. This method used easily accessible starting materials and exhibited broad substrate scope and good functional group tolerance. A wide variety of 2,3,5-triaryl-1*H*-pyrroles were obtained in good to high yields. Because of its potential to generate valuable building motifs in a single step with tandem C−N and C−C bond formations, we anticipate this method of N−H-free pyrrole synthesis will find its applications in medicinal chemistry. Further studies to elucidate the reaction mechanism in detail are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01287.

Detailed experimental procedures, characterization data, and NMR and HRMS spectra for all products (PDF)

Accession Codes

CCDC 2069079 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

#L. Chen and J. Q. Huo contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the National Natural Science Foundation of China (Nos. 32001927 and 31871981), Youth Natural Science Foundation of Hebei Province, China (Nos. B2019204030 and C2020204116), Innovation Team of Modern Agriculture Industry Technology System of Hebei Province (Nos. HBCT2018020205), and Hebei Agricultural University (Nos. 201842 and YJ201963) for financial support. J.M. thanks the National Natural Science Foundation of China (21801128 and 22071107) and Natural Science Foundation of Jiangsu Province, China (BK20170965).

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(18) The source of the proton may come from the intermediate **C** as proposed by Wan and co-workers; for details, please see ref 14a.

https://doi.org/10.1021/acs.orglett.1c01287
Org. Lett. 2021, 23, 4348−4352