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Synthesis of Tetrasubstituted Pyrroles from Terminal Alkynes and Imines

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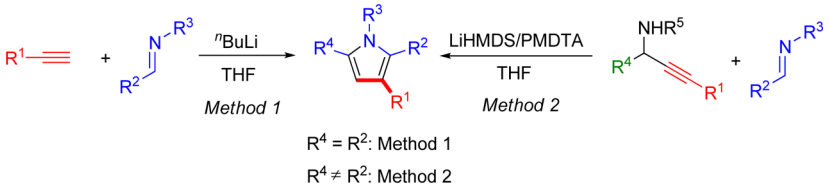
ABSTRACT



Tetrasubstituted pyrroles can be obtained via the reaction of terminal alkynes and imines using ^{n}BuLi as the base in one step with high chemoselectivity (method 1). Alternatively, the intermediate propargylamines can also react with imines to afford tetrasubstituted pyrroles when using LiHMDS as the base (method 2), which provides a complementary method to construct the pyrroles with different substituents.

Pyrroles are not only key structural units in numerous biologically active compounds but also important building blocks in material chemistry.[1] Consequently, their synthetic methods have gained much attention and a lot of amazing progress has been achieved in the past decades.[2] Generally, the construction of the pyrrole ring involves a multistep process from preformed intermediates, such as the classical Knorr, Paal–Knorr, and Hantzsch reactions.[3] Recently, some more efficient and benign approaches, including using new building blocks[4] as well as transition metal catalyzed[5] and multicomponent reactions,[1b,6] have been developed to access multifunctionalized pyrroles. Recently, we have reported the cyclization of 3-aza-1,5-enynes into pyrroles via sulfonyl migration.[4a] As a continuation of our interest in the synthesis of other 3-aza-1,5-enynes, we found that the addition of phenyl acetylene **1a** to *N*-phenyl imine **2a** failed to provide the desired propargylamine (Scheme 1, eq 1). In contrast, tetrasubstituted pyrrole **3a** was obtained unexpectedly as the main product (Scheme 1, eq 2). Considering that terminal alkynes are commercially available and imines can be easily prepared

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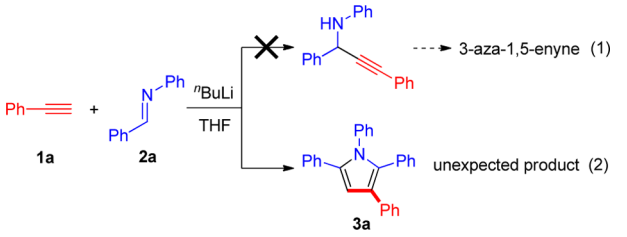
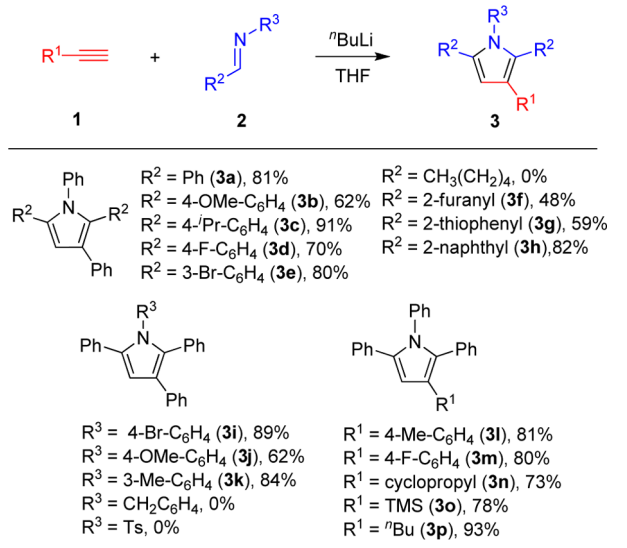
from aldehydes and amines, herein, we reported the first one-step synthesis of tetrasubstituted pyrroles from readily available terminal alkynes and imines with high chemoselectivity.

Scheme 1. New Approach for the Synthesis of Pyrroles



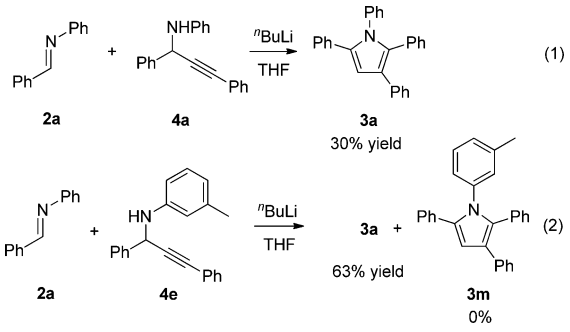
Scheme 2. Synthesis of Tetrasubstituted Pyrroles[a]



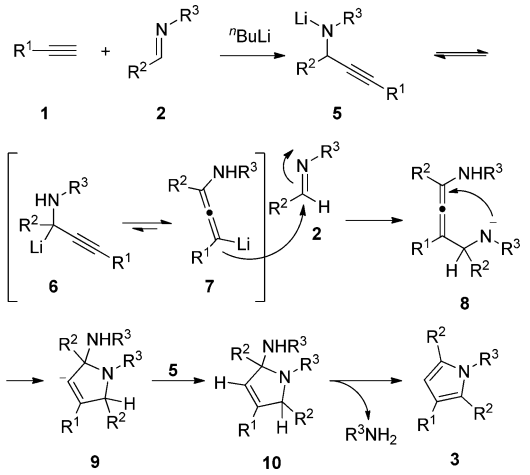
[a] 0.625 mmol of **1**, 1.25 mmol of **2**, 0.625 mmol of ^{n}BuLi, 4 mL of THF, −78 °C for 1 h, rt for 10 h.

Initially, phenylacetylene **1a** and *N*-phenyl imine **2a** were selected as the model substrates to optimize the reaction conditions.[7] We were delighted to find that tetraphenyl pyrrole **3a** was obtained in an acceptable yield when the reaction was conducted in a 1:2 molar ratio (**1a**/**2a**) in the presence of ^{n}BuLi. With this result in hand, the reaction of terminal alkynes **1** with imines **2** was then examined, as shown in Scheme 2. Treatment of phenylacetylene with various aromatic imines **2** afforded the corresponding pyrroles **3** in moderate to excellent isolated yields. Imines **2** with both electron-withdrawing and -donating substituents in R^2 were well tolerated for this process (**3b**−**3e**, 62−80%). In addition, an aryl group (R^2) bearing sterically demanding substituent ^{i}Pr was suitable for the reaction and furnished the product as **3c** in 91% yield. However, when an alkyl substituent was used in R^2, no desired product was observed. To our delight, furanyl and thiophenyl-derived imines underwent this reaction as well and gave the pyrroles **3f** and **3g** in 48% and 59% yield, respectively. Remarkably, 2-naphthaldimine was also tolerated, and the desired product **3h** was afforded in 82% yield. It is noteworthy that this reaction proceeded smoothly only when group R^3 was an aryl substituent (**3i**−**3k**).

Scheme 3. Control Experiments To Probe the Possible Pathway



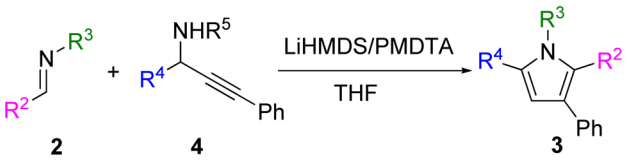
Scheme 4. Proposed Mechanism

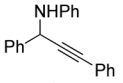
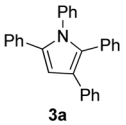
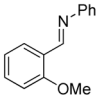
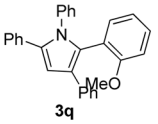
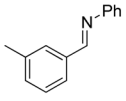
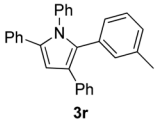
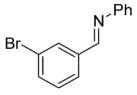
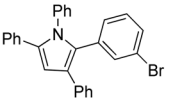
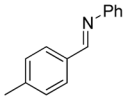
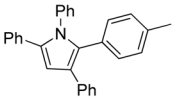
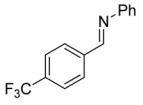
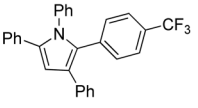
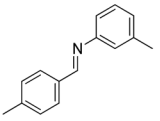
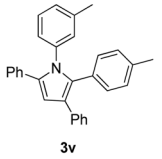
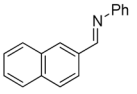
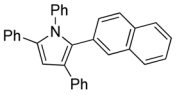
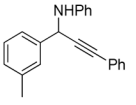
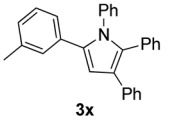
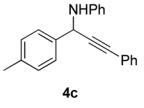
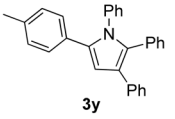
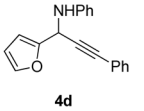
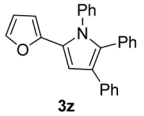
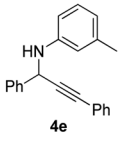
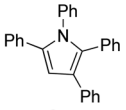


(6) For reviews on multicomponent reactions for the synthesis of pyrroles, see: (a) Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles* **2007**, *73*, 87. (b) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. For some recent examples on multicomponent reactions, see: (c) Bhunia, N.; Das, B. *Synthesis* **2013**, 1045. (d) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (e) Dhara, D.; Gayen, K. S.; Khamarui, S.; Pandit, P.; Ghosh, S.; Maiti, D. K. *J. Org. Chem.* **2012**, *77*, 10441. (f) Attanasi, O. A.; Favi, G.; Mantellini, F.; Moscatelli, G.; Santeusanio, S. *J. Org. Chem.* **2011**, *76*, 2860. (g) Wang, T.; Chen, X.-L.; Chen, L.; Zhan, Z.-P. *Org. Lett.* **2011**, *13*, 3324. (h) Hong, D.; Zhu, Y. X.; Li, Y.; Lin, X. F.; Lu, P.; Wang, Y. G. *Org. Lett.* **2011**, *13*, 4668. (i) Das, B.; Bhunia, N.; Lingaiah, M. *Synthesis* **2011**, 347. (j) Lin, M.; Hao, L.; Ma, R.-D.; Zhan, Z.-P. *Synlett* **2010**, *15*, 2345. (k) Liu, X.-T.; Hao, L.; Lin, M.; Chen, L.; Zhan, Z.-P. *Org. Biomol. Chem.* **2010**, *8*, 3064. (l) Liu, W. B.; Jiang, H. F.; Li, Y.; Huang, L. B. *Org. Lett.* **2010**, *12*, 312. (m) Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674. (n) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090. (o) Naka, H.; Koseki, D.; Kondo, Y. *Adv. Synth. Catal.* **2008**, *350*, 1901. (p) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597. (q) Feng, X.; Wang, Q.; Lin, W.; Dou, G.-L.; Huang, Z.-B.; Shi, D.-Q. *Org. Lett.* **2013**, *15*, 2542.

(7) For the screening of the reaction conditions, please see Supporting Information.

Table 1. Substrate Scope for the Synthesis of Pyrroles[a]



entry	imine	propargyl amine	product	yield (%)[b]
1	 **2a**	 **4a**	 **3a**	78
2	 **2q**	**4a**	 **3q**	86
3	 **2r**	**4a**	 **3r**	83
4	 **2s**	**4a**	 **3s**	79
5	 **2t**	**4a**	 **3t**	86
6	 **2u**	**4a**	 **3u**	66
7	 **2v**	**4a**	 **3v**	73
8	 **2w**	**4a**	 **3w**	86
9	**2a**	 **4b**	 **3x**	86
10	**2a**	 **4c**	 **3y**	83
11	**2a**	 **4d**	 **3z**	50
12	**2a**	 **4e**	 **3a**	76

[a] 0.25 mmol of **2**, 0.5 mmol of **4**, 0.5 mmol of LiHMDS, 0.6 mmol of PMDTA, 4 mL of THF, −78 °C for 1 h, rt for 10 h. [b] Isolated yield.

For terminal alkynes, group R^1 had a slight impact on the reaction; both aryl and alkyl groups provided satisfactory yields for the corresponding pyrroles (**3l**−**3p**, 73−93%).

In view of the fact that two of the substituents in the pyrrole product were from the imine moieties, we suspected that the propargylamine intermediate was possibly first generated in the reaction. To confirm this hypothesis, we synthesized propargylamine **4a** according to the reported method.[8] Fortunately, the same desired product **3a** was indeed observed as we anticipated under the same reaction conditions, albeit with a lower yield (Scheme 3, eq 1). Besides, when propargylamine **4e** was employed to react with imine **2a**, the pyrrole **3a** was found to be the only product (Scheme 3, eq 2). No pyrrole **3m** was detected. This result indicated that the nitrogen atom of the pyrrole originated exclusively from imine **2a** instead of propargylamine **4e**.

On the basis of these observations, a plausible mechanism was suggested as depicted in Scheme 4. Terminal alkyne **1** and imine **2** were first transformed into the intermediate **5** through an addition reaction, which subsequently underwent a 1,2-anion shift to afford propargyllithium reagent **6**. We considered that the intermediate propargyllithium **6** was converted to the allenyllithium **7** by equilibrium.[9] Then allenyllithium **7** reacted with another molecule of imine **2** to form a new intermediate **8**,

(8) (a) Li, C. J.; Wei, C. M. *Chem. Commun.* **2002**, 268. For recent reviews on the synthesis of propargylamines, see: (b) Li, C. J. *Acc. Chem. Res.* **2010**, *43*, 581. (c) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790.

(9) For the equilibria between allenyl−propargyllithium reagents, see: Reich, H. J. *J. Org. Chem.* **2012**, *77*, 5471.

followed by the intramolecular ring closure which resulted in the formation of the cyclized intermediate **9**. Protonation with **5** gave intermediate **10**. Finally, the elimination of aniline from **10** produced the desired product **3**.

From the proposed mechanism, it is easy to find that the pyrroles generated from propargylamines **4** and imines **2** had different groups on the C1 and C4 positions adjacent to the nitrogen atom. Therefore, the reaction of propargylamine **4** and imine **2** may provide a complementary method to obtain tetrasubstituted pyrroles with different substituents.[10] However, the control experiment (Scheme 3, eq 1) revealed that the current reaction conditions were not optimal for the reaction of **4** and **2**. As a consequence, propargylamine **4a** and imine **2a** were selected as the model substrates to optimize the reaction conditions.[7] To our delight, when sterically hindered organolithium reagent bis(trimethylsilyl)amide (LiHMDS) was chosen as the base and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) as the additive, the desired pyrrole **3a** could be afforded in an acceptable yield (Table 1, entry 1).

We further explored the substrate scope of the reaction under the optimized conditions, and the results are shown in Table 1. The scope of groups R^2 and R^4 were mainly explored owing to its advantages over the previous approach. For imines **2**, this reaction tolerated various substituents on the aromatic ring, regardless of the electronic effects and the position of the substituents (Table 1, entries 2−7). Notably, 2-naphthaldimine **2w** was also suitable for this process and the corresponding product **3w** was obtained in 86% yield (entry 8). In addition, the scope of propargylamines **4** was also investigated. The results suggested that both aryl and heterocyclic R^4 substitutions were well tolerated in the reaction (Table 1, entries 9−11). In accordance with the previous observations, the reaction only proceeded smoothly to afford the same desired pyrrole product in good yield when group R^5 was an aryl substituent.

In summary, we have developed an efficient and general protocol for the synthesis of tetrasubstituted pyrroles in just one step from terminal alkynes and imines. Moreover, the direct deprotonation of the preformed propargylamines with imines can be used as a complementary access to afford pyrroles. These two approaches may find applications in the synthesis of various, more complex structures. Further studies to elucidate the reaction mechanism in detail are underway.

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Supporting Information Available. General experimental procedures, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) The reaction of propargyl silyl ethers with imines has been reported to synthesize multisubstituted pyrroles; for details, please see ref 6o.

The authors declare no competing financial interest.