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Synthesis of Pyrroles from Terminal Alkynes, *N*-Sulfonyl Azides, and Alkenyl Alkyl Ethers through 1-Sulfonyl-1,2,3-triazoles

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Supporting Information

ABSTRACT: A method for synthesis of substituted pyrroles has been developed. 1-Sulfonyl-1,2,3-triazoles generated from terminal alkynes gave α-imino rhodium carbene complexes, which when reacted with alkenyl alkyl ethers afforded substituted pyrroles. The method can be efficiently applied to a one-pot sequential reaction starting from terminal alkynes.

Pyrroles are significant structural motifs found not only in valuable bioactive molecules[1] but also in a massive range of natural products.[2] They also find broad applications in supramolecular chemistry and materials science as conjugated polymers.[3] Thus, the development of a streamlined method for their synthesis having a variety of substituents starting from easily available materials is required.[4] Because a sequential reaction is very important from the viewpoint of synthetic efficiency, we herein describe a one-pot sequential method for the synthesis of pyrroles from terminal alkynes, *N*-sulfonyl azides, and alkenyl alkyl ethers (Scheme 1).

Scheme 1. Construction of Pyrroles Starting from Terminal Alkynes, *N*-Sulfonyl Azides, and Alkenyl Alkyl Ethers

Recently, 1-sulfonyl-1,2,3-triazoles, which can be simply generated from a copper-catalyzed 1,3-dipolar cycloaddition reaction of terminal alkynes with *N*-sulfonyl azides,[5] have gained widespread attention as precursors of α-imino metal carbenes.[6] Because the metal carbene species have an inherently electrophilic character, they can react with a wide range of nucleophiles. On the contrary, the nitrogen atom of the α-imino group is nucleophilic in nature to react with various electrophiles. Therefore, these α-imino metal carbenes having both electrophilic and nucleophilic character can easily react with a variety of unsaturated compounds such as nitriles,[7] alkynes,[8] allenes,[9] isocyanates and isothiocyanates,[10] furans,[11] aldehydes,[12] α,β-unsaturated aldehydes,[13] indoles,[14] and arenes[15] to provide the corresponding *N*-heterocyclic compounds. Inspired by these methods, we envisioned the potential of alkenyl alkyl ethers as the reaction partner. We commenced our studies with the reaction of 4-phenyl-1-tosyl-1,2,3-triazole (**1a**) prepared from phenylacetylene and tosyl azide in the presence of CuTC[5b] with ethyl vinyl ether **2a** (Table 1). Treatment of **1a** with **2a** in the presence of $Rh_2(OAc)_4$ (1.0 mol %) in toluene produced 3-phenyl-1-tosylpyrrole **3a** (29%) after 12 h through transannulation followed by elimination of ethanol (entry 1). Gratifyingly, the reaction in chloroform and DCE gave **3a** in quantitative yield (entries 2 and 3). When $Rh_2(OAc)_4$ (0.5 mol %) was used in DCE, the reaction was not completed even if after 12 h (entry 4). Dilution of concentration to 0.5 and 0.2 M afforded only transannulated product **4a**, in 95% and 94% NMR yields, respectively (entries 5 and 6). The unstable dihydropyrrole was converted to the pyrrole **3a** through elimination of ethanol during the column chromatography. Use of **2a** (3 equiv) is crucial for successful results due to low boiling point (entries 3, 7, and 8). $Cu(OAc)_2$ and $Cu(OTf)_2$ as catalyst are totally ineffective (entries 9 and 10).

Table 1. Reaction Optimization[a]

1a + **2a** → (cat., 80 °C, - N_2, - EtOH) → **3a**

entry	cat. (mol %)	solvent	time (h)	yield[b] (%)
1	$Rh_2(OAc)_4$ (1.0)	$PhCH_3$	12	29
2	$Rh_2(OAc)_4$ (1.0)	$CHCl_3$	6	96
3	$Rh_2(OAc)_4$ (1.0)	DCE	3	100 (99)[c]
4	$Rh_2(OAc)_4$ (0.5)	DCE	12	51 (12)[d]
5[f]	$Rh_2(OAc)_4$ (1.0)	DCE	3	(95)[e]
6[g]	$Rh_2(OAc)_4$ (1.0)	DCE	3	(94)[e]
7[h]	$Rh_2(OAc)_4$ (1.0)	DCE	8	57 (15)[d]
8[i]	$Rh_2(OAc)_4$ (1.0)	DCE	8	(83)[d]
9[h]	$Cu(OAc)_2$ (5.0)	DCE	8	(83)[d]
10[h]	$Cu(OTf)_2$ (5.0)	DCE	8	0

[a]Reactions were carried out with **1a** (0.2 mmol) and **2a** (3 equiv) in solvent (0.2 mL, 1.0 M) at 80 °C. [b]NMR yield using CH_2Br_2 as an internal standard. [c]Isolated yield of **3a**. [d]NMR yield of **1a**. [e]NMR yield of **4a**.

4a

[f]DCE (0.4 mL, 0.5 M) was used. [g]DCE (1.0 mL, 0.2 M) was used. [h]**2a** (2 equiv) was used. [i]**2a** (1.5 equiv) was used.

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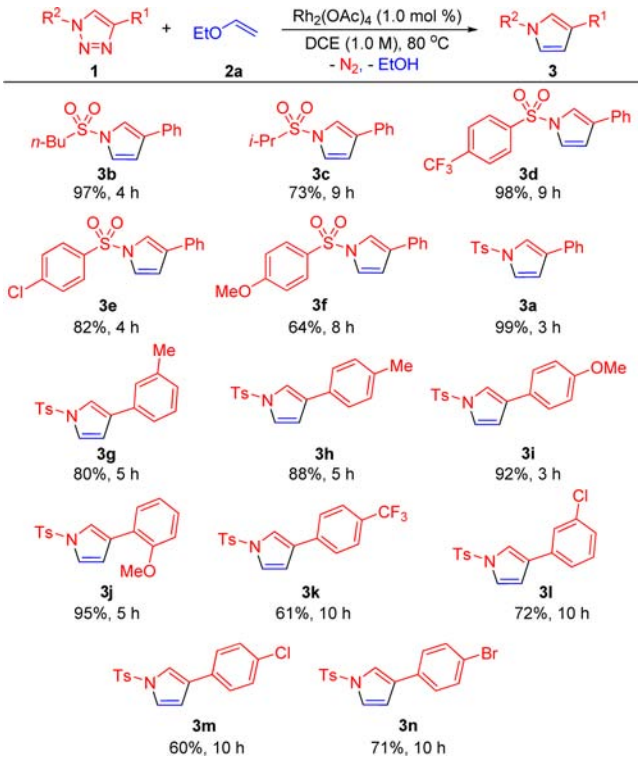
With the optimized conditions in hand, the variation of the sulfonyl group at the N1 of triazoles **1** was studied in the reaction with **2a** using $Rh_2(OAc)_4$ as the catalyst (Scheme 2).

Scheme 2. Rh-Catalyzed Synthesis of Pyrroles Using Various Triazoles[a]

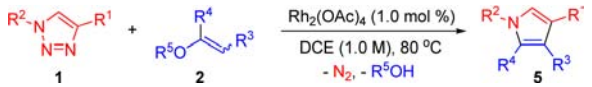


[a]Reactions were carried out with **1** (0.2 mmol) and **2a** (3 equiv) in DCE (0.2 mL, 1.0 M) at 80 °C.

Alkylsulfonyl groups were effective in a one-pot sequential reaction; *n*-butyl- and isopropylsulfonyl triazoles **1b,c** were all adequate substrates. Both electron-withdrawing and -donating substituents were also tolerated on the arylsulfonyl group. Thus, the reaction was well established with respect to the R^2 substituent on the sulfonyl group at N1 of triazoles **1**. Because triazole **1a** obtained from tosyl azide gave the best results, a variety of triazoles **1** having an *N*-tosyl group were subjected to **2a** under the optimum conditions. Triazoles **1g** and **1h** possessing 3-methyl and 4-methyl groups on the phenyl ring at C4 were treated with $Rh_2(OAc)_4$ as the catalyst in DCE for 5 h, producing the corresponding pyrroles **3g** and **3h** in 80% and 88% yields, respectively. An electron-donating methoxy group did not influence the efficiency of the reaction. To our delight, transannulation followed by elimination took place with triazoles **1k**, **1l**, **1m**, and **1n** bearing electron-withdrawing trifluoromethyl, chloro, and bromo groups on the phenyl ring at C4, affording the desired pyrroles **3k**, **3l**, **3m**, and **3n** in yields ranging from 60% and 72%. However, 4-alkyl-substituted 1-tosyl-1,2,3-triazoles did not react with **2a**.[16,17]

To expand the synthetic utility of this reaction, we next examined the affect of substituents of alkenyl alkyl ether on transannulation followed by elimination (Table 2). Subjecting **1a** to 1-ethoxyprop-1-ene (**2b**) and 1-ethoxybut-1-ene (**2c**) gave 1,3,4-trisubstituted pyrroles **5a** and **5b** in 80% and 86% yields, respectively (entries 1 and 2). Treatment of **1a** with (2-ethoxyvinyl)benzene (**2d**) in the presence of Rh catalyst

Table 2. Rh-Catalyzed Synthesis of Pyrroles Using Various Vinyl Ethers[a]



entry	triazole	vinyl enol ether	pyrrole	time (h)	yield (%)
1	**1a**	**2b** (*cis*:*trans* = 2.1:1)	**5a**	5	80
2		**2c** (*cis*:*trans* = 1.5:1)	**5b**	5	86
3		**2d** (*cis*:*trans* = 4.4:1)	**5c**	7	73
4		**2e** (*cis*:*trans* = 1.3:1)	**5d**	4	89[b]
5		**2f** (*cis*:*trans* = 1.7:1)	**5e**	4	75[b]
6		**2g**	**5f**	3	91
7		**2h**	**5g**	4	84[b]
8		**2i**	**5h**	3	77[b]
9		**2j**	**5i**	10	70
10	**1i**	**2b**	**5j**	3	83
11		**2c**	**5k**	4	82
12		**2d**	**5l**	6	71
13		**2g**	**5m**	4	94
14		**2i**	**5n**	2	82[b]

[a]Reactions were carried out with **1** (0.2 mmol) and **2** (3 equiv) in DCE (0.2 mL, 1.0 M) at 80 °C. [b]TMSOTf (5 mol %) was added to reaction mixture after transannulation, and then it was stirred for 30 min.

afforded 3,4-diphenyl-1-tosylpyrrole **5c** in 73% yield (entry 3). When trizole **1a** was treated with 1-(2-ethoxyvinyl)-4-(trifluoromethyl)benzene (**2e**), dihydropyrrole (**4b**) was isolated in 88% yield. Addition of TMSOTf (5 mol %) to the reaction mixture at 25 °C without isolation of **4b** produced **5d** in 89% yield (entry 4). Similarly, 1-chloro-4-(2-(octyloxy)-

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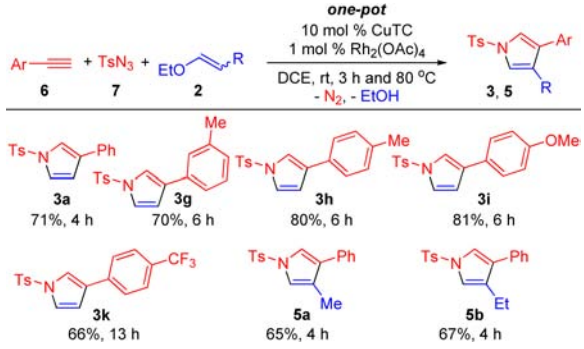
vinyl)benzene (**2f**) was converted to **5e** in 75% yield thorugh transannulation followed by elimination (entry 5). Next, 1-(prop-1-en-2-yloxy)octane (**2g**) and (1-ethoxyvinyl)benzene (**2h**) were used in order to obtain pyrroles having substituent at C2. Delightedly, exposure of **1a** to **2g** produced 2-methyl-4-phenyl-1-tosylpyrrole **5f** in 91% yield (entry 6). We were pleased to obtain **5g** in 84% yield from the reaction of **1a** with **2h** through a one-pot procedure (enrtry 7). The present method worked equally well with 1-ethoxycyclohexene (**2j**) (entry 9). In analogy with **1a**, 4-(4-methoxyphenyl)-1-tosyl-1,2,3-triazole **1i** reacted with alkenyl ethyl ethers **2b–d** having substituents at β-position of double bond to provide 1,3,4-trisubstituted pyrroles **5j–l** in yields ranging from 71% to 83% yields (entries 10–12). 1-Chloro-4-(1-ethoxyvinyl)-benzene (**2i**) was converted to the corresponding pyrroles **5h** (77%) and **5n** (82%) after treatment of TMSOTf (5 mol %) at 25 °C (entries 8 and 14).

As an extension of this work, we next conducted a three-component one-pot synthesis of substituted pyrroles **3** and **5** from terminal alkynes **6** (Scheme 3).[18] Phenylacetylene **6a**

Scheme 3. Synthesis of Pyrroles by Rh-Catalyzed Sequential Reaction[a]

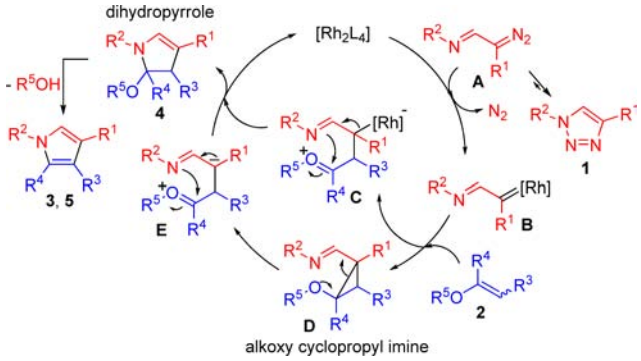


[a]Reactions were carried out with **6** (0.2 mmol), **7** (0.2 mmol), and **2** (3 equiv) in DCE (1.0 mL, 0.2 M).

(0.20 mmol), tosyl azide **7** (0.20 mmol), **2a** (0.6 mmol), CuTC (10 mol %), $Rh_2(OAc)_4$ (1.0 mol %), and DCE (1 mL) were placed in a reaction vessel, and the reaction mixture was stirred at 25 °C. After consumption of both **6a** and **7** for 3 h, the reaction mixture was successively stirred at 80 °C for an additional 4 h. After chromatographic separation, the pyrrole **3a** was obtained in 71% yield. These results indicate that the catalytic amount of copper remaining in the reaction mixture after the first cycloaddition step does not influence largely on the formation and reactivity of the carbenoid. In addition, electron-donating groups such as methyl and methoxy on the phenyl ring worked equally well. Also, 4-ethynyl-α,α,α-trifluorotoluene underwent sequentially cycloaddition, transannulation, and elimination in one-pot, producing **3k** in 66% yield. When **2b** and **2c** were used in the reaction of **6a** and **7**, the corresponding pyrroles **5a** and **5b** were isolated in 65% and 67% yields, respectively.

A plausible mechanism for the formation of pyrrole (**3** and **5**) from 1-sulfonyl-1,2,3-triazole **1** and alkenyl alkyl ether **2** is shown in Scheme 4. First, a reversible ring–chain tautomerization of 1-sulfonyl-1,2,3-triazole **1** gives rise to α-diazo imine **A**.[19] The following irreversible reaction of **A** with rhodium(II) provides α-imino rhodium(II) carbenoid **B** together with liberation of molecular nitrogen. Nucleophilic addition of **2** to

Scheme 4. Plausible Mechanism



the electrophilic carbene center of **B** generates the rhodium-bound zwitterionic intermediate **C**. Then, anionic rhodium of **C** releases an electron pair, which flows into the imine moiety to make the nitrogen atom nucleophilic enough to react cationic oxocarbenium moiety to afford 2,3-dihydropyrrole **4** with regeneration of the rhodium(II) catalyst. Finally, **4** is smoothly transformed to substituted pyrrole **5** through elimination of alcohol. In addition, another pathway can explain the formation of the pyrrole. α-Imino rhodium(II) carbenoid **B** reacts with the electron-rich alkene to provide alkoxy cyclopropyl imine **D**. The presence of the electron-withdrawing *N*-sulfonylimine combined with the electron-donating methoxy group facilitates the cleavage of the cyclopropane ring and generates a stabilized zwitterionic intermediate **E**, which collapses into the corresponding dihyrdopyrrole **4**. However, because the alkoxycyclopropylimine was not observed in NMR studies in DCE-d_4, the intermediate **D** is ruled out in the catalytic cycle (see the Supporting Information).

In conclusion, we have reported the synthetic method of substituted pyrroles from the transannulation of α-imino rhodium carbenes generated in situ from 1-sulfonyl-1,2,3-triazoles with a wide reage of alkenyl alkyl ethers followed by an elimination reaction. Moreover, it has also been demonstrated that pyrroles can be prepared from terminal alkynes, tosyl azide, and alkenyl alkyl ethers through a one-pot sequential reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Professor Ung Chan Yoon (Pusan National University) on the occasion of his honorable retirement.

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