Communication

Rhodium-Catalyzed Conversion of Furans to Highly Functionalized Pyrroles

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Rhodium-Catalyzed Conversion of Furans to Highly Functionalized Pyrroles

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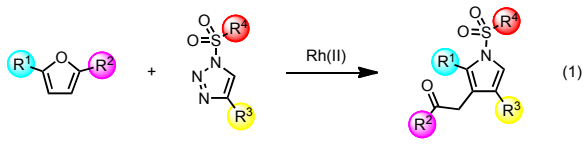
Supporting Information Placeholder

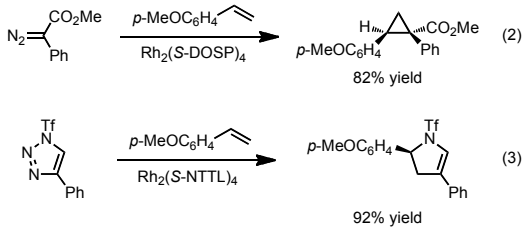
ABSTRACT: The synthesis of highly functionalized pyrroles has been achieved by reaction of rhodium-stabilized imino-carbenes with furans. The reaction features an initial [3+2]-annulation to form bicyclic hemiaminals, followed by ring-opening to generate trisubstituted pyrroles.

Pyrroles are common structural motifs in pharmaceutical agents and smart materials, and development of new methods for their syntheses remains an active field.[1,2] Recent approaches include nitrone/cyclopropane cycloaddition,[2a] 4π–electrocyclizations of azapentadienyl cations,[2b] metallonitrene condensation with aryl acetaldehydes,[2c] tandem photochemical decomposition of α-diazo oximes/formal [3+2]-cycloaddition,[2e] and sequential inter- and intramolecular Buchwald/Hartwig aminations.[2f] In this communication, we describe a novel approach for the synthesis of pyrroles by reaction of *N*-sulfonyltriazoles with furans catalyzed by dirhodium tetracarboxylates (eq 1). In concurrent but independent studies, Sarpong and co-workers have developed a complementary approach to pyrroles by means of intramolecular reactions of *N*-sulfonyltriazoles with allenes.[3]

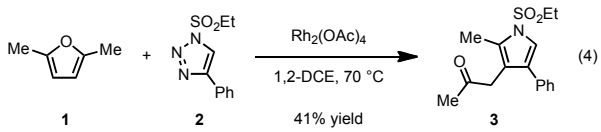


(1)

We have a long-standing interest in the chemistry of rhodium-stabilized donor/acceptor carbenes.[4] The standard method of generating these carbenes has been the rhodium-catalyzed extrusion of nitrogen from diazo compounds.[4] Recently Gevorgyan[5] and Fokin[5c-d,6a] have developed an alternative entry into donor/acceptor carbenes beginning with *N*-sulfonyl-1,2,3-triazoles. We have begun exploring the possibility of using *N*-sulfonyltriazoles to achieve novel rhodium carbene transformations that are inaccessible with the donor/acceptor rhodium carbenes derived from diazo compounds.[7] Typically donor/acceptor rhodium carbenes undergo facile cyclopropanation (eq 2).[8] Therefore, we became intrigued by an anomalous result reported by Fokin on attempted cyclopropanation of *p*-methoxystyrene, which formed a dihydropyrrole (eq 3).[6b]



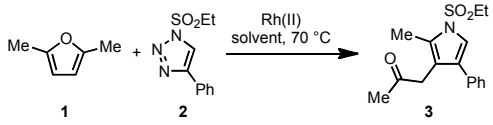
The atypical reaction was observed when *p*-methoxystyrene, an electron rich system, was used as the rhodium carbene trapping agent. Thus, we considered whether other distinct transformations could be achieved from rhodium-catalyzed reactions of triazoles with electron rich heterocycles.[9] We began the study by examining the rhodium acetate-catalyzed reaction of 2,5-dimethylfuran (**1**) with *N*-sulfonyltriazole **2**. We were pleased to find that the reaction resulted in the unprecedented formation of pyrrole **3** in 41% yield.



The conversion of furans and triazoles into pyrroles, containing components coming from both of the original heterocycles, is a novel convergent transformation. Thus, we decided to pursue the optimum conditions and scope of this unusual synthetic sequence. The reaction was found to be highly dependent on both the solvent

and the dirhodium catalyst, as shown in the optimization studies described by Table 1. Initially a number of achiral dirhodium tetracarboxylates were screened (entries 1-6), of which $Rh_2(OOct)_4$ proved superior (entry 3, 56% yield). Highly electron deficient catalysts, such as $Rh_2(TFA)_4$ and $Rh_2(pfb)_4$, did not generate any of the pyrrole and triazole **2** was recovered (entries 5 and 6). A hydrocarbon solvent (entry 7) was substantially less effective than 1,2-dichloroethane (1,2-DCE). The use of chloroform, which has been reported as the optimum solvent for carbenoid transformations from triazoles,[6a] provided poor yields of the desired product (entry 8, 29% yield). We also examined some of the most established chiral catalysts because they often provide improved yields of products over the standard achiral catalysts.[6d, 10] When $Rh_2(S\text{-DOSP})_4$ was implemented, an efficient synthesis of the pyrrole **3** was achieved in 77% yield (entry 9). In contrast, neither of the other amino acid-derived catalysts, $Rh_2(S\text{-NTTL})_4$ and $Rh_2(S\text{-PTAD})_4$, proved as efficacious (entries 10 and 11).

Table 1. Optimization studies for the synthesis of 3[a]



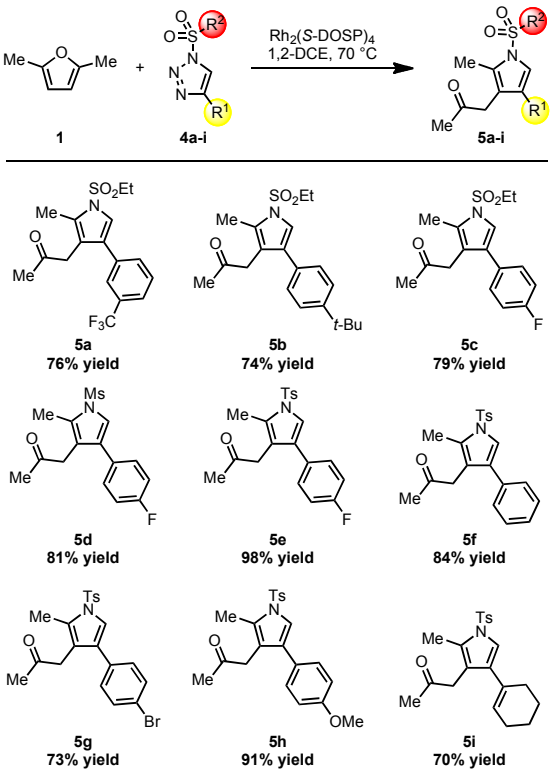
1 2 3

entry	Rh(II)-cat.	solvent	yield[b]
1	$Rh_2(OAc)_4$	1,2-DCE	41
2	$Rh_2(esp)_2$	1,2-DCE	35
3	$Rh_2(OOct)_4$	1,2-DCE	56
4	$Rh_2(OPiv)_4$	1,2-DCE	31
5	$Rh_2(TFA)_4$	1,2-DCE	0[c]
6	$Rh_2(pfb)_4$	1,2-DCE	0[c]
7	$Rh_2(OOct)_4$	$PhCH_3$	42
8	$Rh_2(OOct)_4$	$CHCl_3$	29
9	**$Rh_2(S\text{-DOSP})_4$**	**1,2-DCE**	**77**
10	$Rh_2(S\text{-NTTL})_4$	1,2-DCE	41
11	$Rh_2(S\text{-PTAD})_4$	1,2-DCE	55

[a]**2** (0.25 mmol, 1.0 equiv), **1** (0.75 mmol, 3.0 equiv) and $Rh_2(Lig)_n$ (0.0025 mmol, 0.01 equiv) combined in solvent (1.0 mL) and heated at 70 °C for 4–12 h until consumption of **2** was apparent by TLC. [b]Isolated yields. [c]*N*-Sulfonyltriazole was recovered.

With the optimal conditions in hand, the scope of carbene architecture in the pyrrole synthesis was examined (Table 2). Steric and electronic variations in the 4-aryl moiety on the triazole **4** had minimal impact in the efficacy of the reaction (compare **5a–c** and **5e–h**). A variety of *N*-sulfonyl-protecting groups on the triazole were compatible with pyrrole formation; however, the *N*-tosyl group furnished the highest yields of **5** (compare **5c–e**). The alkenyl triazole **4i**, was also an effective substrate, generating the pyrrole **5i** in 70% yield. This reactivity is in marked contrast to that observed with rhodium vinylcarbenes derived from diazo compounds, as they undergo a tandem cyclopropanation/Cope rearrangement with 2,5-dimethylfuran.[11]

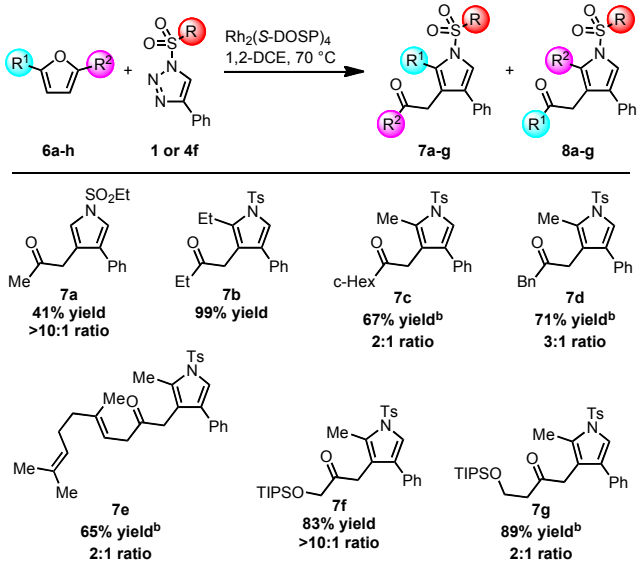
Table 2. *N*-sulfonyltriazole 4 variations[a]



[a]**4** (0.50 mmol, 1.0 equiv), **1** (1.5 mmol, 3.0 equiv) and $Rh_2(S\text{-DOSP})_4$ (9 mg, 0.005 mmol, 0.01 equiv) combined in 1,2-DCE (2.0 mL) and heated at 70 °C for 4–24 h until consumption of **4** was apparent by TLC. Yields are isolated yields of purified products.

The reaction was then extended to a range of furan derivatives (**6**) and the results are summarized in Table 3. Furan itself did not provide a clean transformation, and ring-opened dienal-type products were evident from NMR analysis of the reaction residue.[11] 2-Methylfuran resulted in the formation of a single regioisomer of the 3,4-disubstituted furan **7a** in moderate yield (41%). As with **1**, 2,5-diethylfuran was an excellent substrate for the pyrrole synthesis, furnishing **7b** in 99% yield. The reactions with asymmetrically 2,5-disubstituted furans generally proceeded in high yields (65-89%) but in many instances, mixtures of regiosiomers were formed, as seen with **7c-e** and **7g**. Notably, in the case of 2-(triisopropyl)siloxymethyl-5-methylfuran, the pyrrole **7f** was formed in a highly regioselective manner. Presumably in this case, the combination of steric crowding and electronic deactivation by the C2-substitent causes the reaction to be highly regioselective.

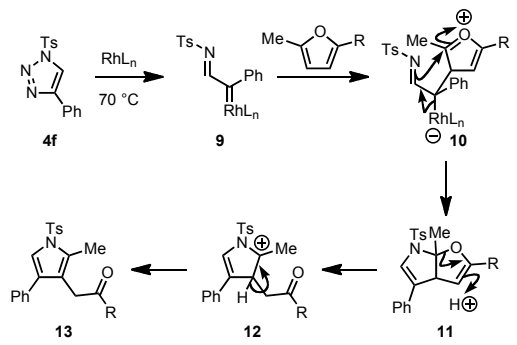
Table 3. Furan 6 variations[a]



[a]**2** or **4f** (0.50 mmol, 1.0 equiv), **6** (1.5 mmol, 3.0 equiv) and Rh_2(*S*-DOSP)$_4$ (9 mg, 0.005 mmol, 0.01 equiv) combined in 1,2-DCE (2.0 mL) and heated at 70 °C for 4–24 h until consumption of **4** was apparent by TLC. Yields are isolated yields of purified products. Ratios (**7**:**8**) determined by ^{1}H NMR analysis of crude reaction residue. [b]Combined yield of two regioisomers **7** and **8**.

A mechanistic rationale for the formation of the pyrroles is provided in Scheme 1. Heating the triazole **4f** in the presence of the dirhodium catalyst generates the imino carbene-intermediate **9** *via* tandem triazole ring-opening and nitrogen extrusion.[6] The rhodium carbene **9** reacts with the furan at C-3 to generate the zwitterion **10**,[9,11] which then closes to the hemiaminal **11**. Ring-opening of **11** under mildly acidic conditions would generate **12**, which is configured to aromatize to the pyrrole **13**. The requirement of attack of the rhodium carbene at the C-3-position would explain why furan failed to give a clean reaction and the yield with 2-methylfuran was modest. Both of these substrates would tend to react with carbenoids at C-2, and the resulting zwitterionic intermediates tend to ring-open to dienones.[9,11]

Scheme 1. Plausible mechanism for pyrrole formation



In summary, we have developed a highly effective synthesis of trisubstituted pyrroles from the rhodium-catalyzed reaction of furans with *N*-sulfonyl-1,2,3-triazoles. The reaction features a formal [3+2]-cycloaddition across the furan C2–C3 π–bond, followed by acid-catalyzed rupture of the transient hemiaminal and termination of the cascade by concomitant elimination/aromatization to generate the pyrrole nucleus.

ASSOCIATED CONTENT

Supporting Information.
Synthetic details and spectral data. 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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ABBREVIATIONS

Rh_2(esp)$_2$, Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]; Rh_2(pfb)$_4$, Dirhodium(II) tetrakis(perfluorobutyrate); Rh_2(*S*-DOSP)$_4$, Dirhodium(II) tetrakis[1-[[4-dodecylphenyl]sulfonyl-(2*S*)-prolinate]; Rh_2(*S*-NTTL)$_4$, Dirhodium(II) tetrakis[*N*-naphthoyl-(*S*)-*tert*-leucinate]; Rh_2(*S*-PTAD)$_4$, Dirhodium (II) tetrakis[*N*-phthaloyl-(*S*)-adamantylglycine]

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(12) Generation of the zwitterion by an initial cyclopropanation followed by ring-opening is unlikely because furanocyclopropanes generated from donor/acceptor rhodium carbenes tend to undergo a second cyclopropanation or a Cope rearrangement (see ref. 9).

SYNOPSIS TOC