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Synthesis of Multifunctionalized 2-Carbonylpyrrole by Rhodium-Catalyzed Transannulation of 1-Sulfonyl-1,2,3-triazole with β-Diketone

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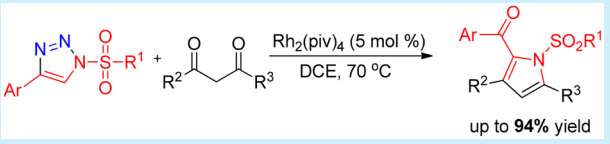
Supporting Information

ABSTRACT: A facile rhodium-catalyzed transannulation of 1-sulfonyl-1,2,3-triazoles with β-diketones was realized, and a series of multisubstituted 2-carbonylpyrroles were synthesized efficiently (up to 94% yield). The protocol features several advantages, such as readily available materials, mild reaction conditions, a concise operating procedure, a broad reaction scope, and excellent regioselectivity when benzoylacetone derivatives were used.



As one of the most valuble heterocycles, pyrrole is the key subunit in a huge number of natural and unnatural compounds, which are widespread in pharmacology and material science.[1] Among these compounds, multisubstituted 2-carbonylpyrrole is a very useful fragment in many drug molecules and liquid crystal materials.[2,3a,b] For instance, ketorolac and tolmetin are both a nonsteroidal anti-inflammatory drug (NSAID) used as an analgesic. The ionophore X-14547 A also shows antibacterial, antitumor, and antihypertensive properties (Figure 1).

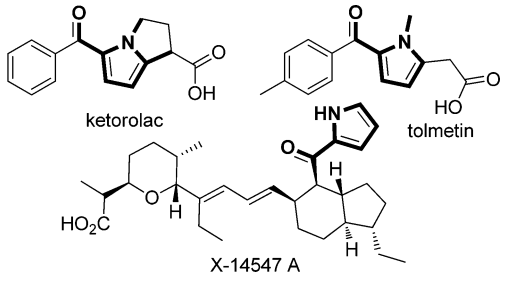
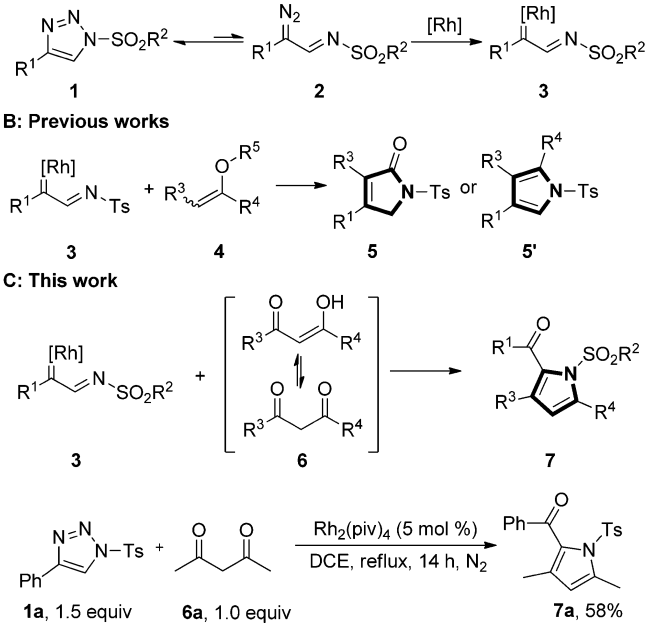


Figure 1. Multisubstituted 2-carbonylpyrrole-derived drugs.

Accordingly, many efficient methodologies for the synthesis of multifunctionalized pyrroles were developed.[1d,3] However, synthetic methods to directly access multisubstituted 2-carbonylpyrrole[4,5] using easily available starting materials under mild reaction conditions are still worth being developed and should be practically useful in the synthesis of such pyrrole derivatives.

In 2008, Gevorgyan and Fokin reported that readily available 1-sulfonyl 1,2,3-triazoles **1** could undergo a Dimorth-type equilibrium to generate an α-diazo imine **2**, and in the presence of a rhodium catalyst, α-imino rhodium carbene **3** could be produced, which underwent formal 3 + 2 cycloaddition with nitriles to give birth to imidazoles (Scheme 1A).[6] The Dimorth-type equilibrium simplified the experimental procedure greatly,

Scheme 1. Proposal of the Transannulation



and moreover, due to the 1,3-dipole feature of the α-imino carbene, plenty of unsaturated compounds could be involved in the transannulation reaction with this triazole to form many nitrogen-containing heterocycles. As a result, an efficient shortcut for the synthesis of nitrogen-containing heterocycles was discovered and large numbers of methodologies based on such an in situ α-imino intermediate were developed.[7−9] Among these reported transformations, the synthesis of pyrroles via an α-imino carbenoid was one of the main fields.[8]

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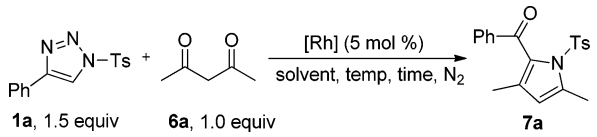
Recently, the Lee group,[8m] Anbarasan group,[8n] Tang group,[8o] and our group[8p] reported that the in situ generated α-imino rhodium carbene **3** could be trapped by enol ether **4** leading to the generation of pyrrole skeleton **5** or **5′** in high yield (Scheme 1B). Notably, in all four previous reports, to establish sufficient nucleophilic activity, the carbonyl group has never been used as a substituent for the alkenyl moiety. It is well-known that β-diketone undergoes an equilibrium with its enol form, and we envisioned that if a much easier available enol, such as **6**, rather than enol ether **4**, was employed to trap the triazole-derived α-imino rhodium carbene **3**, pyrrole skeleton **5′** with a carbonyl at the C-3 position may be produced (R^3 = carbonyl). To our surprise, the reaction of **1a** and **6a** produced pyrrole **7a** with a carbonyl at the C-2 position in 58% yield (Scheme 1C). Considering the utility of the product, the easy availability of the starting material, and the facility of Rh-catalyzed transformation of 1-sulfonyl-1,2,3-triazole, we attempted the reaction and report the achievement herein.

Initially, we attempted the transformation using 4-phenyl-1-tosyl-1*H*-1,2,3-triazole (**1a**),[10] and commercially available acetoacetone (**6a**) as model substrates. Gratifyingly, in a N_2 atmosphere, when **1a** (1.5 equiv) and **6a** (1.0 equiv) reacted in the presence of a catalytic amount of $Rh_2(piv)_4$ (5 mol %) in distilled DCE at 70 °C for 14 h, pyrrole **7a** was generated in excellent yield (94%, Table 1, entry 1). The structure of **7a** was

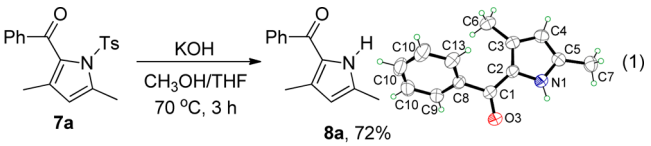
Table 1. Optimization of Reaction Conditions[a]

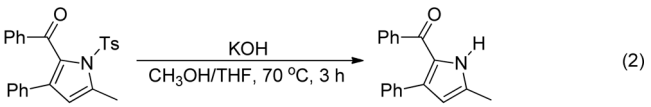


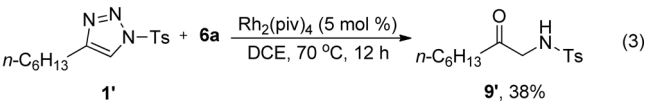
entry	catalyst	solvent	temp/°C	time/h	yield/%[b]
1	**$Rh_2(piv)_4$**	**DCE**	**70**	**14**	**94**
2	$Rh_2(esp)_2$	DCE	70	14	23
3	$Rh_2(oct)_4$	DCE	70	14	31
4	$Rh_2(OAc)_4$	DCE	70	14	trace[c]
5	$Rh_2(tfa)_4$	DCE	70	16	–[c]
6	$Rh_2(piv)_4$	DCM	reflux	14	68
7	$Rh_2(piv)_4$	toluene	70	14	62
8	$Rh_2(piv)_4$	chloroform	reflux	14	60
9	$Rh_2(piv)_4$	DCE	50	12	54
10	$Rh_2(piv)_4$	DCE	reflux	14	58
11	$Rh_2(piv)_4$	DCE	70	5	54
12	–	DCE	70	12	–[d]

[a]General reaction conditions: **1a** (0.3 mmol), **6a** (0.2 mmol), rhodium(II) catalyst (0.01 mmol), solvent (2.0 mL), N_2 atmosphere. [b]Isolated yield. [c]**1a** was decomposed. [d]Without [Rh] catalyst, **1a** recovered in 95% yield. Ts = tosyl, piv = pivalate, esp = $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate, oct = octanoate, OAc = acetate, tfa = trifluoroacetate, DCE = 1,2-dichloroethane, DCM = dichloromethane.

confirmed from the crystal structure of **8a**, which was obtained after tosyl was removed in **7a** (see below, eq 1). Encouraged by this promising result, further screening of the reaction conditions was carried out. Unfortunately, other rhodium catalysts could not improve the yield at all. For example, when $Rh_2(esp)_2$ or $Rh_2(oct)_4$ was utilized as catalyst, the yield of **7a** was only 23% or 31% respectively (entries 2 and 3); **1a** decomposed when $Rh_2(OAc)_4$ or $Rh_2(tfa)_4$ was used (entries 4 and 5). As for solvent, DCE proved to be the most suitable one



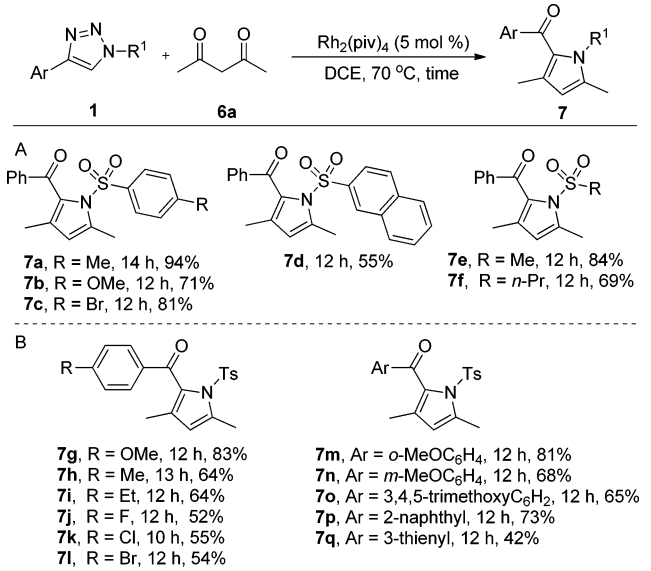




in our investigation. The yields ranged from 60% to 68% when the reaction was carried out in DCM, toluene, and chloroform separately (entries 6–8), which were much less efficient compared to the reaction in DCE. A lower or higher reaction temperature (50 °C or reflux) gave only a moderate yield (54% or 58% respectively, entries 9, 10). Additionally, if the reaction time was reduced to 5 h, the yield decreased to 54% (entry 11). It is worth noting that triazole **1a** was recovered in 95% yield without a catalyst (entry 12), suggesting the crucial role of $Rh_2(piv)_4$. Accordingly, the optimized reaction conditions were established as indicated in entry 1.

With the optimized conditions in hand, the scope of the reaction was evaluated. As revealed in Scheme 2, various

Scheme 2. Triazole Scope of the Reaction



triazoles were tested to react with **6a** in this transannulation. In general, different substituents on the sulfonyl group in triazole **1** influenced the yields greatly (Scheme 2A). For arylsulfonyl-substituted triazoles, the corresponding pyrroles were obtained conveniently in good to excellent yields (**7a–c**, 71–94%, Scheme 2A). However, only a moderate yield (**7d**, 55%) was achieved when the naphthalen-2-ylsulfonyl-substituted triazole was utilized. As for aliphatic sulfonyls, the methyl- and propylsulfonyl-substituted triazoles gave rise to the products in yields of 84% and 69% separately (**7e** and **7f**).

Different substituents on the 4-poisition of triazoles also had a great impact on the yield of the corresponding products

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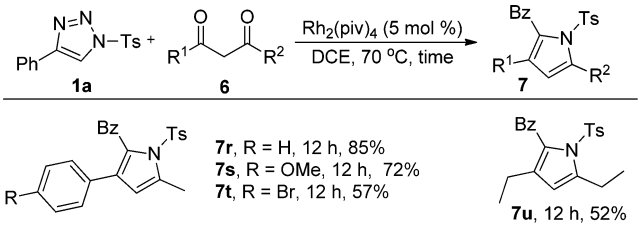
(Scheme 2B). For 4-aryl substituted triazoles, the substrates bearing electron-donating groups at the *p*-position of the phenyl group produced the desired pyrroles (**7g–i**, 64–83%) in higher yields than the ones with electron-withdrawing groups (**7j–l**, 52–55%); *o*-$MeOC_6H_4$ substituted triazole **1m** gave product **7m** in 81% yield because of the same electronic effect compared to its *p*-$MeOC_6H_4$ substituted isomer; when *m*-$MeOC_6H_4$ substituted triazole **1n** was utilized, the yield of **7n** was decreased to 68%, which was coincident with electron-rich cases (**7h** and **7i**) and still higher than those electron-poor cases (**7j–l**). However, when a highly electron-rich group was introduced into the triazole, taking 3,4,5-trimethoxyphenyl substituted triazole **1o** as an example, the yield of **7o** was decreased to 65%. Additionally, the 2-naphthyl substituted triazole worked well in this reaction and the corresponding product **7p** was generated in 73% yield. Notably, a biheteroaryl ketone is a very important motif found in medicinal molecules.[11] When 4-(thiophen-3-yl) substituted triazole **1q** was employed, 4-(thiophen-3-yl)-1*H*-pyrrole **7q** could be generated concisely under our mild reaction conditions in 42% yield.

We then investigated the scope of the *β*-diketone derivatives **6** (Scheme 3). Excellent regioselectivity was observed when

Scheme 3. *β*-Diketone Scope of the Reaction

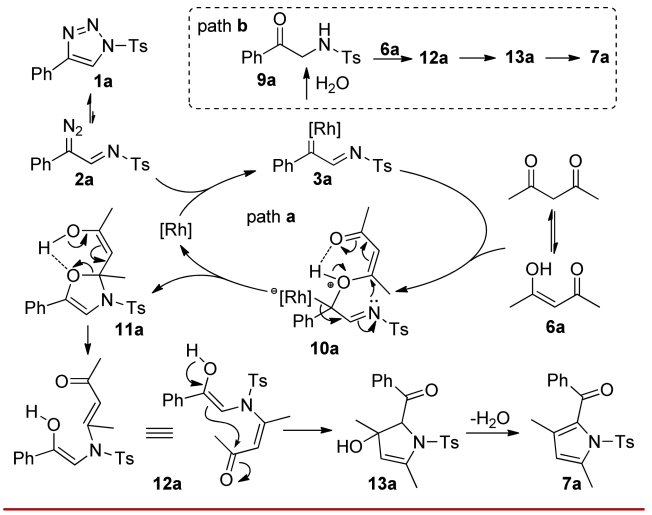


benzoylacetones were involved in this reaction. Only the 3-aryl-5-methyl substituted pyrroles **7r–t** were generated in moderate to good yields (**7r**, 85%; **7s**, 72%; **7t**, 57%), and no corresponding 3-methyl-5-aryl pyrroles were detected. The structures of **7r–t** were inferred by comparison of the NMR data of **8r** in the literature,[12] and **8r** was obtained by removing the tosyl group in **7r** (see below, eq 2). Compared to **6a**, heptane-3,5-dione performed less efficiently (**7u**, 52%).

In addition, when 3-*n*-hexyl-1,2,3-triazole **1′** was used in this reaction, no desired pyrrole was obtained and only hydrolysis product **9′** was isolated in 38% yield (eq 3).

The proposed mechanism of this rhodium-catalyzed transannulation is displayed in Scheme 4.[8m,n] *α*-Imino diazo compound **2a** was formed by the Dimorth-type rearrangement of triazole **1a**, and *α*-imino rhodium carbene **3a** was generated subsequently in the presence of a rhodium catalyst, which then was attacked by the nucleophilic enol **6a** and produced zwitterionic intermediate **10a**. Subsequent addition–elimination reactions finished the catalytic cycle and produced compound **12a** through **11a**, an aldol reaction of **12a** resulted in the formation of **13a**, and then aromatization of **13a** by dehydration gave pyrrole **7a** (path a). Alternatively, since hydrolysis product **9** was isolated as a byproduct in some cases, path b was proposed as another possible reaction pathway. In path b, **9a** was generated from the hydrolysis of **3a**, and then condensation of **9a** and **6a** could produce **12a**, which would furnish **7a** finally.[13] However, when **9a** was introduced into the reaction, taking the place of **1a** under the standard reaction conditions, no desired **7a** was generated and **9a** was recovered

Scheme 4. Proposed Mechanism



in 91% yield. This excluded path b preliminarily. When benzoylacetones were used, excellent regioselectivity was observed. This may be because, under the standard reaction conditions, the substrate, taking **6r** (1-phenylbutane-1,3-dione) as example, more likely exists as an enol form of (*Z*)-3-hydroxy-1-phenylbut-2-en-1-one instead of the other one, that is, (*Z*)-4-hydroxy-4-phenylbut-3-en-2-one. Thus, the regioselective product 3-phenyl pyrrole **7r**, rather than the 5-phenyl pyrrole isomer, was obtained.[14]

In summary, a facile rhodium catalyzed transannulation of 1-sulfonyl-1,2,3-triazole with *β*-diketone was achieved, demonstrating once again the potential of such a triazole in organic synthesis. This transformation tolerated common functional groups well, and high chemoselectivity ensured pyrroles as the main products rather than other products. Excellent regioselectivity was also observed when benzoylacetone derivatives were used. More importantly, carbonyl substituted enol was used for the first time to trap *α*-imino carbene, offering much more flexibility in pyrrole synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03179.

Experimental procedures, characterization data, and NMR spectra for new compounds (PDF)
Crystal data of **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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