LETTERS

Rhodium(II)-Catalyzed Formal [3 + 2] Cycloaddition of *N*-Sulfonyl-1,2,3-triazoles with Isoxazoles: Entry to Polysubstituted 3-Aminopyrroles

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Supporting Information

ABSTRACT: A novel rhodium(II)-catalyzed formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with isoxazoles has been achieved that provides an efficient method for the synthesis of polysubstituted 3-aminopyrrole derivatives. An operationally simple one-pot synthesis of the titled compounds from terminal alkynes, tosyl azide, and isoxazoles was also



developed. The presented reaction affords an illustrative example of employing 1,2,3-triazoles as the [2C]-component in relevant cycloaddition reactions.

N-Sulfonyl 1,2,3-triazoles have recently emerged as capable precursors for the synthesis of various nitrogen heterocycles.¹ Upon treatment with rhodium(II) catalysts, *N*-sulfonyl 1,2,3-triazoles readily undergo denitrogenative reaction to form Rh(II)–azavinylcarbene (Rh–AVC, Scheme 1a), a versatile intermediate that could promote a wide range of transformations. Thus far, the applications of Rh–AVC as [1C]- or

Scheme 1. Rh(II)-Carbene-Promoted Formal [3 + 2] and [3 + 3] Cycloadditions



aza-[3C]-synthons in cycloaddition reactions have been well explored.^{2,3} However, its potential as a [2C]-synthon remains underdeveloped. In early 2015, we disclosed a novel Rh(II)-catalyzed transannulation of *N*-sulfonyl 1,2,3-triazoles with 2*H*-azirines, which allowed the divergent synthesis of polysub-stituted 3-aminopyrroles and 1,2-dihydropyrazines, respectively, via formal [3 + 2] and [3 + 3] cycloadditions (Scheme 1a).⁴ Notably, two highly relevant works were independently reported by Shi and Lee.⁵ The above studies^{4,5a} represent the first two examples of the application of Rh–AVC as a [2C]-synthon in cycloaddition reactions, thus opening new prospects for the emerging area of research.

Isoxazoles represent a class of important heterocycles in organic synthesis.⁶ Great efforts have been made to develop new methods for their preparation.⁷ In turn, they could also serve as precursors for the synthesis of other valuable scaffolds.⁸ Indeed, one of the key structural elements of isoxazoles relies on the fact that they possess a relatively labile N–O bond that could be readily cleaved and then integrated into a new heterocycle.^{8a–c} As a paradigm, Davies recently developed an intriguing Rh(II)-catalyzed transannulation of isoxazoles with vinyl diazo compounds.^{8a} In this reaction, the isoxazole partner reacts with Rh–vinylcarbene (Rh–VC) to form an isoxazolium ylide intermediate, which then undergoes sequential ring-opening with cleavage of the N–O bond, 6π electrocyclization, and oxidative dehydrogenation to afford polysubstituted pyridine (Scheme 1b). In view of the resemblance between

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the above-mentioned Rh–AVC and Rh–VC species, we assumed that a Rh(II)-catalyzed aza-[3 + 3] cycloaddition between *N*-sulfonyl 1,2,3-triazoles and isoxazoles could be also feasible, which would lead to 1,2-dihydropyrazine derivatives (Scheme 1c). As a part of our continuing interest on the development of novel transformations for the synthesis of heterocycles of biological importance,^{4,9} we report herein the progress we have achieved on this subject. Interestingly, while the originally proposed chemistry failed to work as expected, a novel [3 + 2] cycloaddition was discovered in practice, which resulted in highly functionalized 3-aminopyrroles as products (Scheme 1c).

We commenced our studies by treatment of 1-tosyl-1*H*-1,2,3-triazole **1a** (1.5 equiv) and 5-phenyl-3-propylisoxazole **2a**¹⁰ (1.0 equiv) with 1.5 mol % of $Rh_2(oct)_4$ in 1,2-DCE at 140 °C. The starting materials were consumed quickly, providing a major product in 47% isolated yield. However, careful analysis of the NMR spectroscopic data of the product showed that it was not the expected dihydropyrazine product but a 3-amino-4-acylpyrrole derivative, as represented by the structure of **3a** (Table 1). This discovery, despite being unexpected, deserved

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N=	=N+ N(C Rh(II) (1.5 mol % 1,2-DCE	⁶⁾ TsHN	Ph
Ph		other condition	s Ph	Ме
1.5 e	a 2a quiv) (1.0 ec	quiv)	H 3a	
entry	catalyst	temp (°C)	time	yield ^b (%)
1	$Rh_2(oct)_4$	140	30 min	47
2	$Rh_2(OAc)_4$	140	30 min	24
3	$Rh_2(S-DOSP)_4$	140	30 min	trace
4	$Rh(S-PTAD)_4$	140	30 min	trace
5	$Rh_2(esp)_2$	140	30 min	84
6	$Rh_2(esp)_2$	140	3 h	<10
7	$Rh_2(esp)_2$	120	1 h	65
8	$Rh_2(esp)_2$	160	30 min	41
9 ^c	$Rh_2(esp)_2$	140	30 min	81
10	$Rh_2(esp)_2$	140, microwave	10 min	78
11 ^d	$Rh_2(esp)_2$	140	30 min	44

^{*a*}Reaction conditions: **1a** (0.30 mmol), **2a** (0.20 mmol), and Rh(II) cat. (3.0 μ mol) in DCE (1.0 mL). ^{*b*}Isolated yield. ^{*c*}4 Å molecular sieves was used. ^{*d*}1:1 ratio of **1a**/**2a** was employed. DCE = dichloroethane, oct = octanoate, (*S*)-DOSP = 4-(dodecylphenyl)-sulfonyl-(2S)-prolinate, (*S*)-PTAD = *N*-phthaloyl-(*S*)-adamantylglycine, esp = $\alpha, \alpha, \alpha, \alpha$ -tetramethyl-1,3-benzenedipropanoate.

further investigation, since the resulting polysubstituted 3aminopyrroles represent a class of unique structural element distributed in various natural products and bioactive molecules,¹¹ and thus, the development of new methods for their synthesis has been a subject of significant interest.¹² Moreover, the *N*-sulfonyl 1,2,3-triazole 1a involved in this reaction serves as a [2C]- rather than commonly seen aza-[3C]-component, which showcases the great potential of Rh–AVC as a versatile synthon.

To improve the efficiency of the above transformation, we conducted a systematic condition screening with **1a** and **2a** as standard substrates. First, the effect of Rh(II) catalyst was examined. It was shown that while Rh₂(oct)₄, Rh₂(S-DOSP)₄, and Rh(S-PTAD)₄ led to poor conversion (entries 2–4), Rh₂(esp)₂¹³ displayed superior reactivity to afford an excellent yield of **3a** (84%, entry 5). This observation was in agreement

with our previous results.⁴ We also found that the reaction temperature had a notable influence on the outcomes. Both lower and higher temperatures than 140 °C gave inferior results (entries 6-8). In addition, we attempted to conduct the reaction in the presence of 4 Å molecular sieves or microwave irradiation; however, no improvement could be made (entries 9 and 10). Finally, it turned out that the use of 1.5 equiv of 1,2,3-triazole was required to ensure satisfactory results since a decreased yield was obtained when a 1:1 ratio of 1a/2a was employed in the reaction (entry 11).

Having the optimal conditions in hands, we sought to evaluate the generality of the reaction. First of all, a broad range of 4-aryltriazoles were evaluated with 2a as the reactant partner (Scheme 2). It was shown that all of the examined reactions

Scheme 2. Scope of 1,2,3-Triazoles^{a,b}



"Reaction conditions: 1 (0.30 mmol), 2a (0.20 mmol), and $Rh_2(esp)_2$ (3.0 μ mol) in DCE (1.0 mL) at 140 °C. ^bIsolated yield.

worked smoothly to provide the corresponding products in good to acceptable yields. The substrates bearing electrondonating or -withdrawing substituents were well tolerated, although the former generally gave a slightly higher yields than the latter. The orientation of the substitute also showed some impact on the efficacy, while the *para-* and *meta-*substituted substrates gave better results than the *ortho-*substituted ones (**3e** vs **3f**; **3g** vs **3h**). Moreover, the reaction could be applied to the triazoles bearing other aromatic rings, as shown by the case of **3i** and **3j**. However, when some 4-alkyltriazoles were submitted to the current conditions, they failed to give satisfying results (structures not shown). Of note, the structure of **3e** was unambiguously determined by X-ray crystallog-raphy.¹⁴

Next, the scope of the isoxazole partner was also systematically evaluated, as shown in Scheme 3. Not surprisingly, an array of 3-alkyl-5-arylisoxazoles exhibited reactivity similar to that of 2a and provided the corresponding products 3l-o in

Scheme 3. Scope of Isoxazoles a,b



^aReaction conditions: 1a (0.30 mmol), 2 (0.20 mmol), and Rh₂(esp)₂ (3.0 μ mol) in DCE (1.0 mL) at 140 °C. ^bIsolated yield.

good yields. Moreover, 3-aryl-5-alkylisoxazoles also proved to be suitable substrates for the transformation, although in some cases the yields were moderate (e.g., 3s and 3t). This transformation could also be extended to 3,5-diarylisoxazoles and 3,5-dialkylisoxazoles, as shown by the cases of 3u-y. Notably, the substrate bearing an alkenyl substituent on the C-5 position of 2 was also tolerated, which further extended the substrate scope of the method. However, both monosubstituted (e.g., 5-methylisoxazole) and trisubstituted isoxazoles (e.g., 3,5dimethyl-4-phenylisoxazole) failed to give promising results under the present conditions (results not shown).

To simplify the operation of above transformations, we also developed a one-pot protocol for the synthesis of *N*-aminopyrrole derivatives from terminal alkynes, tosyl azide, and isoxazoles. As a proof of concept, phenylacetylene 4 was treated with TsN_3 in the presence of CuTC (3.0 mol %) in 1,2-DCE at room temperature for 4 h. The resulting mixtures, without isolation, were further treated with isoxazole 2a (0.7 equiv) and $Rh_2(esp)_2$ (1.5 mol %) at 140 °C for 30 min, which afforded 3a in 77% yield (entry 1, Table 2). This one-pot protocol was also applied to some other terminal alkynes (4b and 4c) and isoxazoles (2h, 2n, and 2o). Gratifyingly, all of them gave satisfying yields that are comparable to those obtained in the stepwise reactions (entries 2–6).

Finally, a plausible mechanism for the title reaction is depicted in Scheme 4. Thus, Rh–AVC A, once generated from 1,2,3-triazole 1, could react 2 to form isoxazolium ylide B, which then underwent ring opening with cleavage of the N–O bond to form azatriene C. At this point, there are two possibilities for C to evolve into different products. In the path

Table 2. One-Pot Synthesis of 3-Aminopyrroles^a

R—	P	T	TsN ₃	1	2	>		
	4	CuTC (3.0 mol %) 1,2-DCE, rt, 4 h		•	Rh ₂ (esp) ₂ (1.5 m 140 °C, 30 mi	ol %) n	Ū	
entry	alkyı	ne		isoxa	zole	prod	uct: yield ^l (%)	,
1	4a: R = I	Ph	2a : $R_2 = r$	-C ₃ H	$r_3; R_3 = Ph$	3	3a: 77	
2	4b : R = 4 Ph	4-Me-	2a			3	3b : 72	
3	4c: R = 4 Ph	1- <i>t</i> Bu-	2a			3	3c : 82	
4	4a		2h : $R_3 = 4$ C_4H_9	1-MeC	D-Ph; $R_2 = n$ -	3	3r : 63	
5	4a		2n : $R_3 = 1$	$R_2 = N$	Лe	3	3x : 54	
6	4a		20 : $R_3 = n$	$-C_5H_1$	1; $R_2 = n - C_4 H_9$	3	3y : 80	

^aReaction conditions: 4 (0.50 mmol), TsN_3 (0.50 mmol), and CuTc (15.0 μ mol) in DCE (1.5 mL); then 2 (0.33 mmol), Rh(II) catalyst (5.0 μ mol). ^bIsolated yield.

Scheme 4. Plausible Mechanisms



A, it may convert into 1,2-dihydropyrazine **D** via a 6 π electrocyclization, as we have originally imagined. Alternatively, **C** could undergo a 5-*exo-trig* cyclization between the nucleophilic C-4 and electrophilic C-3, thus affording zwitterionic intermediate **E**.¹⁵ After proton transfer followed by tautomerization, **E** could advance to the final product **G**. Interestingly, while path A takes place predominantly in the reaction reported by Davies (Scheme 1b),^{8a} path B appears favorable in the current scenario, most likely attributed to the presence of a highly electrophilic imine moiety in the intermediate **C**. In this context, the inherent nature of Rh–AVC endows it some unique reactivity distinct from its all-carbon counterpart, that is, the Rh–VC species.

In summary, we have developed a novel Rh(II)-catalyzed formal [3 + 2] cycloaddition of *N*-sulfonyl-1,2,3-triazoles with isoxazoles, which enables the rapid access of polysubstituted *N*-aminopyrroles from the readily available precursors. The presented chemistry, in conjunction with the precedent,^{4,5a} clearly illustrates the attractive potential of Rh–AVC as [2C]-synthon in cycloaddition reactions. Efforts to develop new reactions following this direction are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b02570.

Experimental procedures, spectral data, and spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For leading reviews, see: (a) Chattopadhyay, B.; Gevorgyan, V. Angew. Chem., Int. Ed. 2012, 51, 862. (b) Gulevich, A. V.; Gevorgyan, V. Angew. Chem., Int. Ed. 2013, 52, 1371. (c) Davies, H. M. L.; Alford, J. S. Chem. Soc. Rev. 2014, 43, 5151.

(2) For selected examples of Rh-AVC as a [1C]-synthon, see: (a) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. J. Am. Chem. Soc. 2009, 131, 18034. (b) Grimster, N.; Zhang, L.; Fokin, V. V. J. Am. Chem. Soc. 2010, 132, 2510. (c) Zibinsky, M.; Fokin, V. V. Org. Lett. 2011, 13, 4870. (d) Alford, J. S.; Davies, H. M. L. Org. Lett. 2012, 14, 6020. (e) Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. J. J. Am. Chem. Soc. 2012, 134, 194. (f) Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami, M. Angew. Chem., Int. Ed. 2013, 52, 3883. (g) Chuprakov, S.; Worrell, B. T.; Selander, N.; Sit, R. K.; Fokin, V. V. J. Am. Chem. Soc. 2014, 136, 195.

(3) For selected examples of Rh-AVC as an aza-[3C]-synthon, see: (a) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. J. Am. Chem. Soc. 2008, 130, 14972. (b) Miura, T.; Yamauchi, M.; Murakami, M. Chem. Commun. 2009, 45, 1470. (c) Chattopadhyay, B.; Gevorgyan, V. Org. Lett. 2011, 13, 3746. (d) Schultz, E. E.; Sarpong, R. J. Am. Chem. Soc. 2013, 135, 4696. (e) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. Org. Lett. 2013, 15, 3298. (f) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. J. Am. Chem. Soc. 2013, 135, 4652. (g) Parr, B. T.; Green, S. A.; Davies, H. M. J. J. Am. Chem. Soc. 2013, 135, 4716.

(4) Wang, Y. H.; Lei, X. Q.; Tang, Y. F. Chem. Commun. 2015, 51, 4507.

(5) For [3 + 2] cycloadditions of 1,2,3-triazoles with 2*H*-azirines, see: (a) Zhao, Y. Z.; Yang, H. B.; Tang, X. Y.; Shi, M. *Chem. - Eur. J.* **2015**, 21, 3562. For [3 + 3] cycloadditions, see: (b) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376.

(6) For leading reviews on this topic, see: (a) Hu, F.; Szostak, M. Adv. Synth. Catal. 2015, 357, 2583. (b) Pinho e Melo, T. M. V. D. Curr. Org. Chem. 2005, 9, 925.

(7) For selected recent examples, see: (a) Schmitt, D. C.; Lam, L.; Johnson, J. S. Org. Lett. **2011**, 13, 5136. (b) Zheng, H.; McDonald, R.; Hall, D. G. Chem. - Eur. J. **2010**, 16, 5454. (c) Jackowski, O.; Lecourt, T.; Micouin, L. Org. Lett. **2011**, 13, 5664. (d) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. Chem. - Eur. J. **2014**, 20, 11101. (e) Kankala, S.; Vadde, R.; Vasam, C. S. Org. Biomol. Chem. **2011**, 9, 7869. (f) Zhu, X.; Wang, Y. F.; Ren, W.; Zhang, F. L.; Chiba, S. Org. Lett. **2013**, 15, 3214.

(8) For selected examples, see: (a) Manning, J. R.; Davies, H. M. J. Am. Chem. Soc. 2008, 130, 8602. (b) Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fettinger, J. C.; Tantillo, D. J.; Kurth, M. J. Org. Lett. 2013, 15, 2062. (c) Zhou, A. H.; He, Q.; Shu, C.; Yu, Y. F.; Liu, S.; Zhao, T.; Zhang, W.; Lu, X.; Ye, L. W. Chem. Sci. 2015, 6, 1265. (d) Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. Angew. Chem., Int. Ed. 2011, 50, 7803. (e) Liu, X. L.; Han, W. Y.; Zhang, X. M.; Yuan, W. C. Org. Lett. 2013, 15, 1246. (f) Takikawa, H.; Takada, A.; Hikita, K.; Suzuki, K. Angew. Chem., Int. Ed. 2008, 47, 7446.

(9) (a) Shang, H.; Wang, Y.; Tian, Y.; Feng, J.; Tang, Y. Angew. Chem., Int. Ed. 2014, 53, 5662. (b) Tian, Y.; Wang, Y. H.; Shang, H.; Xu, X. D.; Tang, Y. F. Org. Biomol. Chem. 2015, 13, 612. (c) Feng, J.; Wang, Y. H.; Li, Q. G.; Jiang, R. W.; Tang, Y. F. Tetrahedron Lett. 2014, 55, 6455. (d) Wang, Y. H.; Lei, X. Q.; Tang, Y. F. Synlett 2015, 26, 2051.

(10) Hansen, T. V.; Wu, P.; Fokin, V. V. J. Org. Chem. 2005, 70, 7761. For details of the preparation of other isoxazoles presented in this study, see the Supporting Information.

(11) For selected reviews, see: (a) Baraldi, P. G.; Preti, D.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R. Bioorg. Med. Chem. 2007, 15, 17.
(b) Bando, T.; Sugiyama, H. Acc. Chem. Res. 2006, 39, 935. For selected examples, see: (c) De Rosa, M.; Arnold, D.; Hartline, D. J. Org. Chem. 2013, 78, 8614. (d) Kanakis, A. A.; Sarli, V. Org. Lett. 2010, 12, 4872. (e) Dose, C.; Farkas, M. E.; Chenoweth, D. M.; Dervan, P. B. J. Am. Chem. Soc. 2008, 130, 6859. (f) Schneider, K.; Keller, S.; Wolter, F. E.; Roeglin, L.; Beil, W.; Seitz, O.; Nicholson, G.; Bruntner, C.; Riedlinger, J.; Fiedler, H. P.; Süessmuth, R. D. Angew. Chem., Int. Ed. 2008, 47, 3258. (g) LoVerme, J.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Stella, N.; Xu, C.; Tarzia, G.; Piomelli, D. Bioorg. Med. Chem. Lett. 2009, 19, 639.

(12) For selected examples, see: (a) Marcotte, F. A.; Lubell, W. D. Org. Lett. 2002, 4, 2601–2603. (b) Attanasi, O. A.; Favi, G.; Filippone, P.; Golobic, A.; Stanovnik, B.; Svete, J. J. Org. Chem. 2005, 70, 4307. (c) Sasada, T.; Sawada, T.; Ikeda, R.; Sakai, N. Eur. J. Org. Chem. 2010, 4237. (d) Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. J. Org. Chem. 2006, 71, 6996.

(13) (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. J. Am. Chem. Soc. 2004, 126, 15378. (b) Zalatan, D. N.; Du Bois, J. J. Am. Chem. Soc. 2009, 131, 7558.

(14) CCDC 1421308 (3e) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data request/cif.

(15) Some other processes might also account for the conversion of C to E, such as a 4π conrotory electrocyclization followed by ring expansion.