Communication

Rhodium-Catalyzed Transannulation of 1,2,3-Triazoles with Nitriles

Tony Horneff, Stepan Chuprakov, Natalia Chernyak, Vladimir Gevorgyan, and Valery V. Fokin

J. Am. Chem. Soc., **2008**, 130 (45), 14972-14974 • DOI: 10.1021/ja805079v • Publication Date (Web): 15 October 2008

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S COMMUNICATIONS

Published on Web 10/15/2008

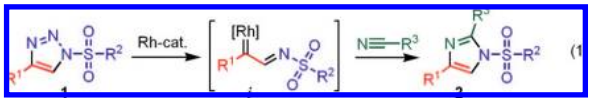
Rhodium-Catalyzed Transannulation of 1,2,3-Triazoles with Nitriles

Tony Horneff,[†] Stepan Chuprakov,[†] Natalia Chernyak,[‡] Vladimir Gevorgyan,*[,‡] and Valery V. Fokin*[,†]

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

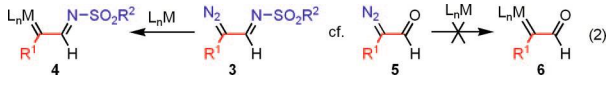
Received July 2, 2008; E-mail: vlad@uic.edu; fokin@scripps.edu

Discovery of the copper-[1] and ruthenium-catalyzed[2] azide−alkyne cycloaddition reactions reinvigorated interest in 1,2,3-triazoles. However, even a cursory survey of the literature reveals that in most reports utilizing this chemistry, 1,2,3-triazoles remain reactivity culs-de-sac: permanent inert connectors that unite molecular fragments with a desired function.[3] This is not surprising when one takes into account the exceptional stability of these nitrogen heterocycles: they are exceedingly resistant to thermal degradation and are not affected by severe hydrolytic, reductive, and oxidative conditions.[4] Herein, we wish to report that Rh(II) complexes catalyze ring opening of *N*-sulfonyl 1,2,3-triazoles **1** to form Rh-iminocarbenoids ***i***, which, upon reaction with nitriles, produce imidazoles **2** in good to excellent yields (eq 1).



(1)

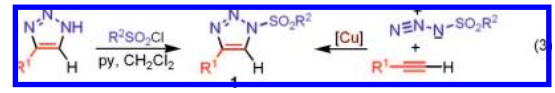
We envisioned that 1-sulfonyl triazoles **1** could serve as precursors to the diazoimine species **3** that, in turn, could be converted to metal carbenoids **4** (eq 2). Rhodium carbenoids exhibit the wealth of reactivity,[5] and this method of generating their diazo progenitors is particularly attractive considering that sulfonyl triazoles effectively become synthetic equivalents of α-diazo aldehydes **5**, which, understandably,[6] cannot be converted to the corresponding rhodium carbenoids **6**.



(2)

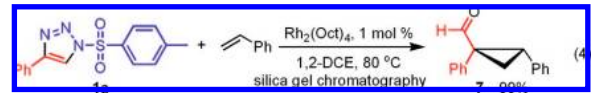
A related ring-chain isomerization of 7-halo pyridotriazoles to (2-pyridyl) diazoalkanes was recently exploited in the rhodium-catalyzed reactions with alkynes and nitriles yielding indolizines and imidazopyridines, respectively.[7] These transannulation processes are remarkably efficient and exhibit excellent scope with respect to the nitrile and alkyne components.

1-(*p*-Toluenesulfonyl)triazoles **1** used in our study can be prepared by tosylation of the parent NH-triazoles[8] (eq 3). However, reactions of NH-triazoles with other sulfonyl chlorides often produced mixtures of N-1 and N-2 sulfonylated products, requiring careful tuning of the reaction conditions. Copper-catalyzed cycloaddition of sulfonyl azides with terminal alkynes, instead, is a more direct and reliable route to the desired 1-sulfonyl triazoles. Recent improvements in the selectivity of this reaction[4e,9] make it an even more convenient alternative to the NH-triazole route.



(3)

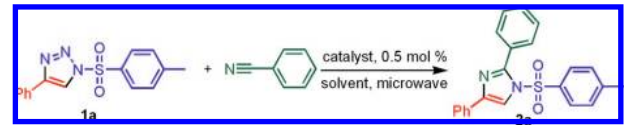
When 1-toluenesulfonyl 4-phenyl 1,2,3-triazole **1a** was treated at 80 °C with dirhodium(II) octanoate in the presence of styrene, trans-cyclopropane carboxaldehyde **7** was obtained in nearly quantitative yield with >20:1 trans-selectivity[10] (eq 4), thus confirming our hypothesis that reactive rhodium-carbenoid species could be obtained from sulfonyl triazoles. Evidently, aldehyde **7** originated from the corresponding tosylimine upon hydrolysis during column chromatography on silica gel.



(4)

Encouraged by this result, we attempted a transannulation reaction of triazole **1a** with benzonitrile under a number of conditions (Table 1). Triazole **1a** was readily transformed into the *N*-tosyl imidazole **2a** in 51% yield when the reaction was performed in the microwave synthesizer at 140 °C for 15 min using 0.5 mol % of rhodium(II) acetate dimer. No special precautions to exclude atmospheric oxygen were taken (entry 1). A screen of other catalysts revealed that the electron-deficient rhodium(II) heptafluorobutyrate and trifluoroacetate were significantly less active (entries 2 and 3).

Table 1. Reaction of 1-(*p*-Toluenesulfonyl)-4-phenyl-1,2,3-triazole with Benzonitrile: Effect of the Catalyst, Solvent, and Temperature



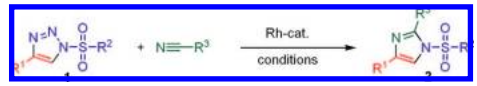
entry	catalyst	solvent	*t*, °C	time	yield, %[a]
1	$Rh_2(OAc)_4$	$CHCl_3$	140	15 min	51
2	$Rh_2(CF_3COO)_4$	$CHCl_3$	140	15 min	0[b]
3	$Rh_2(C_3F_7COO)_4$	$CHCl_3$	140	15 min	<5
4	**$Rh_2(Oct)_4$**	**$CHCl_3$**	**140**	**15 min**	**82**
5	**Rh_2(*S*-DOSP)$_4$**	**$CHCl_3$**	**140**	**15 min**	**83**
6	-	$CHCl_3$	140	15 min	0[b]
7	$Rh_2(Oct)_4$	CH_2Cl_2	160	15 min	0[c]
8	$Rh_2(Oct)_4$	CH_2Cl_2	140	15 min	77
9	$Rh_2(Oct)_4$	CH_2Cl_2	120	30 min	70
10	$Rh_2(Oct)_4$	CH_2Cl_2	100	30 min	43
11	$Rh_2(Oct)_4$	1,2-DCE	140	15 min	73
12	$Rh_2(Oct)_4$	toluene	140	15 min	55
13	$Rh_2(Oct)_4$	hexane	140	15 min	71
14	$Rh_2(Oct)_4$	THF	140	15 min	0[d]
15	$Rh_2(Oct)_4$	PhCl	140	15 min	62

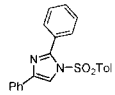
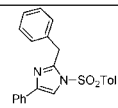
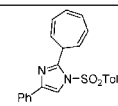
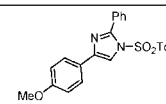
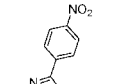
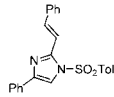
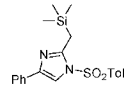
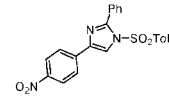
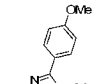
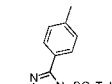
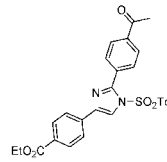
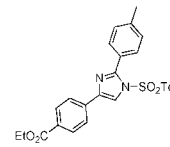
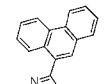
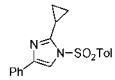
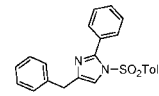
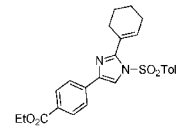
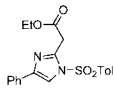
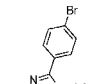
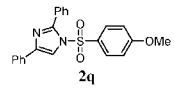
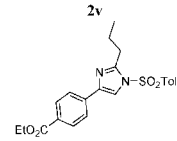
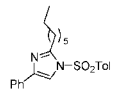
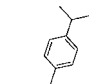
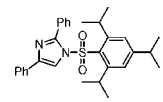
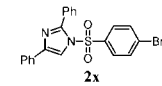
[a] Isolated yield. [b] Only starting material observed. [c] Only decomposition observed. [d] Besides starting material, (*Z*)-2-phenyl-4-tosyl-5,6,7,8-tetrahydro-4H-1,4-oxazocine observed.[11]

[†] The Scripps Research Institute.
[‡] University of Illinois at Chicago.

10.1021/ja805079v CCC: $40.75

Table 2. Rh-Catalyzed Transannulations of 1-Sulfonyl Triazoles with Nitriles



entry	product	yield,%[a]	entry	product	yield,%[a]	entry	product	yield,%[a]	entry	product	yield,%[a]
1	 **2a**	82[b] 85[c]	7	 **2g**	71[b] 94[c]	13	 **2m**	67[b]	19	 **2s**	64[c]
2	 **2b**	69[b] 76[c]	8	 **2h**	76[b]	14	 **2n**	99[c]	20	 **2t**	88[b]
3	 **2c**	72[b] 87[c]	9	 **2i**	80[c]	15	 **2o**	51[c]	21	 **2u**	88[c]
4	 **2d**	77[b]	10	 **2j**	77[c]	16	 **2p**	42[b]	22	 **2v**	74[c]
5	 **2e**	44[b]	11	 **2k**	95[c]	17	 **2q**	76[b]	23	 **2w**	83[c]
6	 **2f**	70[b]	12	 **2l**	82[b]	18	 **2r**	65[b]	24	 **2x**	72[b]

[a] Isolated yield. [b] General procedure A: $Rh_2(Oct)_4$ (0.5 mol %), $CHCl_3$, 15 min at 140 °C/MW. [c] General procedure B: $Rh_2(S\text{-DOSP})_4$ (0.5 mol %), DCE, 12−24 h at 80 °C (see Supporting Information for details).

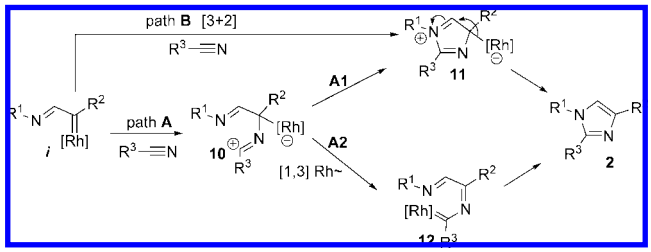
Gratifyingly, rhodium(II) octanoate catalyst provided 82% yield of imidazole **2a**, and $Rh_2(S\text{-DOSP})_4$ was equally effective (entries 4 and 5). Further elevation of temperature resulted in the formation of intractable mixtures of products (entry 7), whereas temperatures below 120 °C led to significantly lower conversion and yields (entry 9 and 10). Halogenated solvents (chloroform, dichloromethane, and 1,2-dichloroethane) were superior to THF, toluene, and hexane (entries 1, 8, 11−15).

When performed with conventional heating at 80 °C under inert atmosphere, the reaction proceeded to completion in 15 h and furnished imidazole **2a** in 83% yield. These experiments led to the formulation of two general procedures (described in detail in Supporting Information): procedure A, in which the reaction is performed in the microwave synthesizer at 140 °C in chloroform and procedure B, which utilizes conventional heating and 1,2-dichloroethane as a solvent.

Next, we examined the scope of the reaction with respect to the nitrile component. As illustrated by the examples shown in Table 2, a broad range of nitriles efficiently participated in the transannulation reaction. For example, aromatic (Table 2, e.g., entries 1−4), alkyl (entries 5−7, 10, 13, 14, 23), and alkenyl (entries 8, 22) nitriles were competent reactants, providing 1-sulfonyl imidazole products in very good yields. Electron-deficient nitriles were less reactive than electron-rich ones (cf. entries 1 and 2). In addition, the reaction appears to be quite insensitive to both steric and electronic variations of the sulfonyl group. Thus, 4-methoxy- and 2,4,6-triisopropyl, and 4-bromobenzenesulfonyl triazoles were equally reactive furnishing imidazoles in good yields (entries 17, 18, 24). In contrast, the nature of the substituent at C4 of the triazole has a significant effect on the reaction. Aromatic groups were preferred to aliphatic, and more electron deficient substituents (cf. entries 20 and 21) imparted higher reactivity to the triazole. Reactivity of 4-benzyl triazole (entry 16) is another noteworthy example because α-alkyl diazoacetates are known to undergo ready β-hydride elimination.[12] In our conditions, this pathway was not dominant, although 26% of 4-methyl-*N*-(3-phenylallylidene)benzenesulfonamide (2.4:1 *E*:*Z*) was observed. Benzene ring expansion, another potential side reaction, was not observed.[13]

The copper(I)-catalyzed synthesis of 1-sulfonyl triazoles and their subsequent transannulation with nitriles can be combined into a one-pot two-step synthesis, thus further simplifying the experimental procedure (eq 5). The catalytic amount of copper remaining in the reaction mixture after the first step evidently does not interfere with the formation or reactivity of the carbenoid. Thus, we successfully prepared 1-(*p*-toluenesulfonyl) imidazole **2a** by combining tosyl azide and phenylacetylene in chloroform in the presence of 1 mol % of the copper(I) thiophene-2-carboxylate catalyst,[14] and after 14 h the reaction mixture was treated with 3 equiv of benzonitrile and

Scheme 1



1.25 mol % of $Rh_2(Oct)_4$ at 140 °C for 15 min. Chromatographic separation furnished the imidazole product in 52% overall yield.

(5)

The 1-sulfonyl 2,4-disubstituted imidazoles (**2a**) can be easily converted to the parent N*H* compounds, such as **8** (eq 6), by treatment with hydroxybenzotriazole. Additionally, alkylation of **2a** at N3 results in the facile conversion to 1,2,5-trisubstituted imidazoles **9**.

(6)

We have not yet performed extensive investigations of the mechanism of this transannulation reaction. However, it is probably mechanistically related to the analogous annulation of nitriles with diazoketones reported by Helquist and Akermark,[15] and we propose the following mechanistic possibilities (Scheme 1). In pathway A, a nucleophilic attack of a nitrile at the Rh-carbenoid ***i***[16] leads to the ylide **10**, which upon cyclization (path A1) into a zwitterion **11**, and subsequent metal loss, produces imidazole **2**. Alternatively, ylide **10** may give rise to the Rh-carbenoid **12** via a 1,3-Rh-shift (path A2). Subsequent cyclization of **12**, followed by the reductive elimination,[17] furnishes **2**. A possible direct formation of **11** via a cycloaddition of ***i*** with a nitrile (path B) cannot be ruled out at this time.

Reported here is a new, highly modular two-step synthesis of imidazoles wherein three new carbon−nitrogen bonds of the imidazole heterocycle are formed in a two-step sequence which begins from alkynes, sulfonyl azides, and nitriles.[18] Dinitrogen is the only byproduct of the reaction. In addition, we have demonstrated for the first time that stable and readily accessible *N*-sulfonyl 1,2,3-triazoles are convenient precursors to reactive metal carbenoids and can be viewed as surrogates of the α-diazo imines. Rhodium carbenoids obtained in this fashion are synthetic equivalents of the putative α-formyl carbenoids and should be useful analogs of the better known donor−acceptor substituted carbenoid family. Mechanistic studies and investigation of the scope of their reactivity are currently underway in our laboratories.

Acknowledgment. We thank Dr. Jessica Raushel (TSRI) for help with the CuTC-catalyzed synthesis of sulfonyl triazoles and Mr. Frank W. Hwang (UIC) for technical assistance. This work was supported by the National Institutes of Health (Grant GM-64444, VG; DA-19372, VVF) and the Skaggs Institute for Chemical Biology and Pfizer, Inc. (SC, VVF).

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

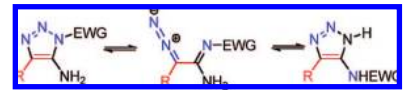
References

(1) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(2) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (b) Boren, B.; Narayan, S.; Rasmussen, L. K.; Jia, G.; Fokin, V. V. *ORGN-365*; ACS national Meeting, 232nd, San Francisco, CA, Sept. 10−14, 2006; ACS: Washington, DC, 2006. (c) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680. (d) Oppilliart, S.; Mousseau, G.; Zhang, L.; Jia, G.; Thuery, P.; Rousseau, B.; Cintrat, J.-C. *Tetrahedron* **2007**, *63*, 8094. (e) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

(3) (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *n/a*, 51. (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (c) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7.

(4) One notable exception are those which bear a strong electron-withdrawing group, such as cyano-, nitro-, or sulfonyl at N-1. These triazoles are known to undergo facile ring opening to diazoimine tautomers. The ring-chain tautomerism manifests itself in various interconversions of triazoles and other heterocycles, collectively known as Dimroth rearrangements. (a) Dimroth, O. *Ann.* **1909**, *364*, 183. (b) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33. For example, 1-aryl-5-amino-1,2,3-triazoles readily interconvert with 5-arylamino-1,2,3-triazoles. The facility of the ring opening is primarily controlled by the substituent at N-1; the acidity of the solvent and the nature of the functional groups at C-4 and C-5 influence the equilibrium between the triazole isomers. Metallation at C-5



further destabilizes 1-sulfonyl triazoles. Thus, 5-cuprated 1-sulfonyl triazoles are normally short lived at room temperature and readily extrude a molecule of dinitrogen producing ketenimines, versatile intermediates which react with nucleophiles including amines, water, alcohols, and imines. The 5-lithiated triazoles decompose already at−78 °C; see: (c) Whiting, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3157. (d) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (e) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 3154. (f) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (g) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347.

(5) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (d) Doyle, M. P. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Jr., Eds.; Wiley: New York, 2004; pp 561−592.

(6) Fu, G. C. In *Modern Rhodium Catalyzed Organic Reactions*; Evans, D. A., Ed.; VCH: Weinheim, Germany, 2005, pp 79.

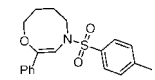
(7) (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) For a related Rh-catalyzed cyclopropenation of pyridotriazoles, see: Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463.

(8) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171.

(9) (a) Yoo, E. J.; Ahlquist, M.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520. (b) Raushel, J.; Fokin, V. V.,unpublished work.

(10) This cyclopropanation reaction proceeded with >20:1 trans-selectivity, similarly to the analogous Rh-catalyzed [2 + 1] cycloadditions of diazocarbonyl compounds with alkenes (see refs 5a−c for additional examples).

(11) After heating for additional 30 min at 140 °C, the starting material was completely consumed, and (*Z*)-2-phenyl-4-tosyl-5,6,7,8-tetrahydro-4H-1,4-oxazocine in 22% yield was isolated.



(12) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908.

(13) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22.

(14) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Innitzer, A. *Synlett* **2005**, *n/a*, 2405.

(15) Connell, R.; Scavo, F.; Helquist, P.; Akermark, B. *Tetrahedron Lett.* **1986**, *27*, 5559.

(16) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761.

(17) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642.

(18) Synthesis of imidazoles review: Grimmett, M. R. In *Science of Synthesis*; Neier, R., Ed.; Thieme: New York, 2002; Vol. 12, p 325.

JA805079V