

Published in final edited form as:

J Am Chem Soc. 2008 November 12; 130(45): 14972–14974. doi:10.1021/ja805079v.

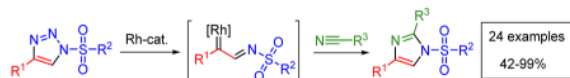
Rhodium-Catalyzed Transannulation of 1,2,3-Triazoles with Nitriles

 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

[‡]Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

E-mail: Tony HorneffStepan ChuprakovNatalia ChernyakVladimir Gevorgyan [vlad@uic.edu] Valery V. Fokin [fokin@scripps.edu]

Abstract



Stable and readily available 1-sulfonyl triazoles are converted to the corresponding imidazoles in good to excellent yields via a rhodium(II)-catalyzed reaction with nitriles. Rhodium iminocarbenoids are proposed intermediates.

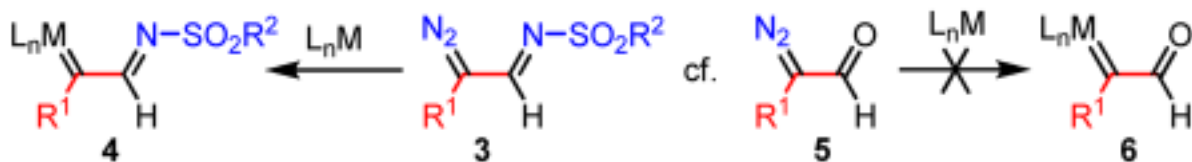
Discovery of the copper-¹ and ruthenium-catalyzed² azide-alkyne cycloaddition reactions reinvigorated interest in 1,2,3-triazoles. However, even a cursory survey of the literature reveals that in most reports utilizing this chemistry, 1,2,3-triazoles remain reactivity cul-de-sac: permanent inert connectors 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

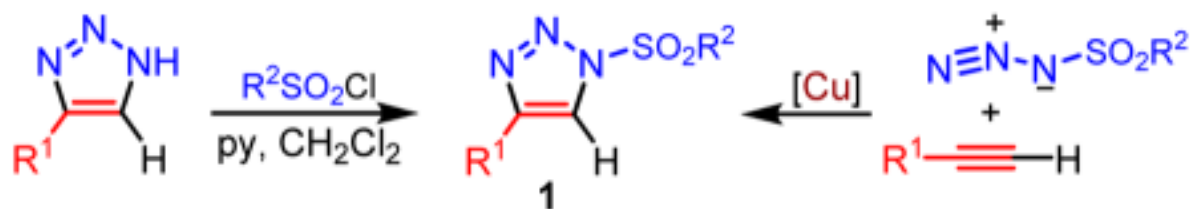
attractive considering that sulfonyl triazoles effectively become synthetic equivalents of α -diazo aldehydes **5**, which, understandably,⁶ cannot be converted to the corresponding rhodium carbenoids **6**.



(2)

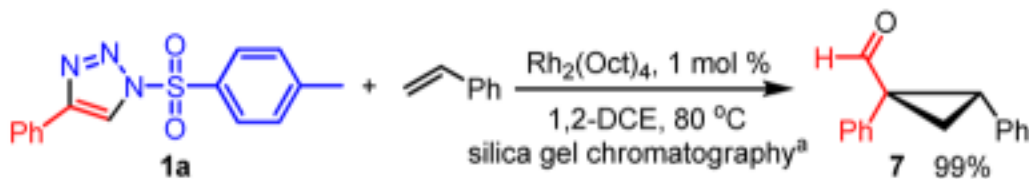
A related ring-chain isomerization of 7-halo pyridotriazoles to (2-pyridyl) diazoalkanes was recently exploited in the rhodium-catalyzed reactions with alkynes and nitriles yielding indolizines and imidazopyridines, respectively.⁷ These transannulation processes are remarkably efficient and exhibit excellent 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-triazoles⁸ (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*-selectivity¹⁰ (eq. 4), thus confirming our hypothesis that reactive rhodium-carbenoid species could be obtained from sulfonyl triazoles.



^a Evidently, aldehyde **7** originated from the corresponding tosylimine upon hydrolysis during column chromatography on silica gel.

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). Gratifyingly, rhodium(II) octanoate catalyst provided 82% yield of imidazole **2a**, and Rh₂(*S*-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 eq of benzonitrile and 1.25 mol % of Rh₂(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 *NH* 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

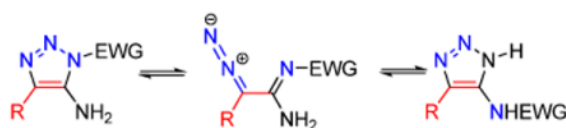
We thank Dr. Jessica Raushel (TSRI) for help with the CuTC-catalyzed synthesis of sulfonyl triazoles and Mr. Frank W. Hwang (UIC) for technical assistance. This work was supported by the National Institutes of Health (GM-64444, VG; DA-19372, VVF) and the Skaggs Institute for Chemical Biology and Pfizer,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

References

- (a) Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew Chem Int Ed* 2002;41:2596. (b) Tornøe CW, Christensen C, Meldal M. *J Org Chem* 2002;67:3057. [PubMed: 11975567]
- (a) Zhang L, Chen X, Xue P, Sun HHY, Williams ID, Sharpless KB, Fokin VV, Jia G. *J Am Chem Soc* 2005;127:15998. [PubMed: 16287266] Boren, B.; Narayan, S.; Rasmussen, LK.; Jia, G.; Fokin, VV. 232nd ACS National Meeting; San Francisco, CA, United States. Sept. 10-14, 2006; ORGN-365 (c) Majireck MM, Weinreb SM. *J Org Chem* 2006;71:8680. [PubMed: 17064059] (d) Oppillart S, Mousseau G, Zhang L, Jia G, Thuery P, Rousseau B, Cintrat JC. *Tetrahedron* 2007;63:8094. (e) Boren

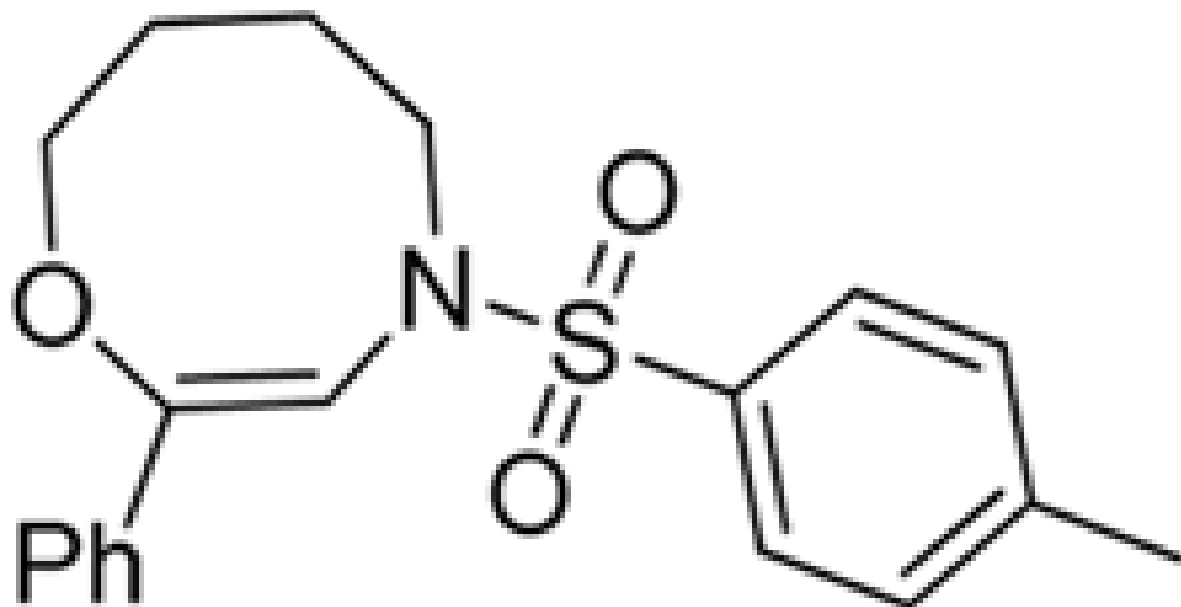
BC, Narayan S, Rasmussen LK, Zhang L, Zhao H, Lin Z, Jia G, Fokin VV. *J Am Chem Soc* 2008;130:8923. [PubMed: 18570425]

3. (a) Bock VD, Hiemstra H, van Maarseveen JH. *Eur J Org Chem* 2006:51. (b) Moses JE, Moorhouse AD. *Chem Soc Rev* 2007;36:1249. [PubMed: 17619685] (c) Wu P, Fokin VV. *Aldrichimica 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 TL, Gymer GE. *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.

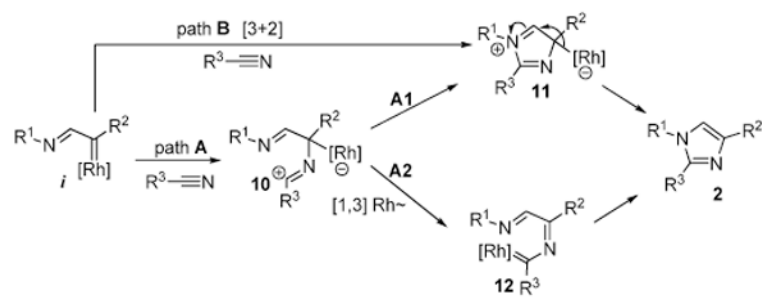


Metallation at C-5 further destabilizes 1-sulfonyl triazoles. Thus, 5-cuprated 1-sulfonyl triazoles are normally short lived at room temperature and readily extrude a molecule of dinitrogen producing ketenimines, versatile intermediates which react with nucleophiles including amines, water, alcohols, and imines. The 5-lithiated triazoles decompose already at $-78\text{ }^{\circ}\text{C}$. See (c) Whiting M, Fokin VV. *Angew Chem Int Ed* 2006;45:3157. (d) Bae I, Han H, Chang S. *J Am Chem Soc* 2005;127:2038. [PubMed: 15713069] (e) Cassidy MP, Raushel J, Fokin VV. *Angew Chem Int Ed* 2006;45:3154. (f) Cho SH, Yoo EJ, Bae I, Chang S. *J Am Chem Soc* 2005;127:16046. [PubMed: 16287290] (g) Yoo EJ, Bae I, Cho SH, Han H, Chang S. *Org Lett* 2006;8:1347. [PubMed: 16562888]

- (e) Cassidy MP, Raushel J, Fokin VV. *Angew Chem Int Ed* 2006;45:3154. (f) Cho SH, Yoo EJ, Bae I, Chang S. *J Am Chem Soc* 2005;127:16046. [PubMed: 16287290] (g) Yoo EJ, Bae I, Cho SH, Han H, Chang S. *Org Lett* 2006;8:1347. [PubMed: 16562888]
5. (a) Davies HML, Beckwith REJ. *Chem Rev* 2003;103:2861. [PubMed: 12914484] (b) Davies HML. *Angew Chem Int Ed* 2006;45:6422. (c) Doyle MP, Forbes DC. *Chem Rev* 1998;98:911. [PubMed: 11848918] Doyle, MP. *Reactive Intermediate Chemistry*. Moss, RA.; Platz, MS.; Jones, M., Jr, editors. Wiley; New York: 2004. p. 561-592.
6. Fu, GC. *Modern Rhodium Catalyzed Organic Reactions*. Evans, DA., editor. VCH; Weinheim: 2005. p. 79
7. (a) Chuprakov S, Hwang FW, Gevorgyan V. *Angew Chem Int Ed* 2007;46:4757. (b) Chuprakov S, Gevorgyan V. *Org Lett* 2007;9:4463. [PubMed: 17892296] for a related Rh-catalyzed cyclopropanation of pyridotriazoles, see
8. Kalisiak J, Sharpless KB, Fokin VV. *Org Lett* 2008;10:3171. [PubMed: 18597477]
9. (a) Yoo EJ, Ahlquist M, Bae I, Fokin VV, Sharpless KB, Chang S. *J Org Chem* 2008;73:5520. [PubMed: 18557650] (b) Raushel J, Fokin VV. unpublished
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 $140\text{ }^{\circ}\text{C}$, 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.



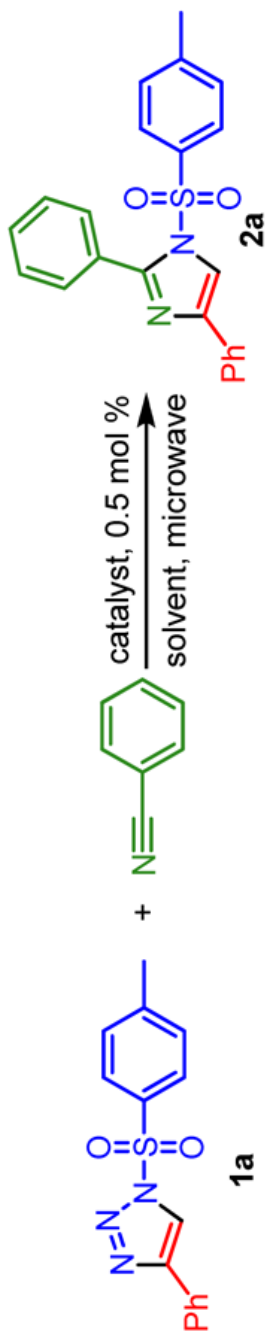
12. Taber DF, Herr RJ, Pack SK, Geremia JM. *J Org Chem* 1996;61:2908. [PubMed: 11667136]
13. Panne P, Fox JM. *J Am Chem Soc* 2007;129:22. [PubMed: 17199269]
14. (a) Allred GD, Liebeskind LS. *J Am Chem Soc* 1996;118:2748. (b) Innitzer A. *Synlett* 2005:2405.
15. Connell R, Scavo F, Helquist P, Akermark B. *Tetrahedron Lett* 1986;27:5559.
16. Doyle KJ, Moody CJ. *Tetrahedron* 1994;50:3761.
17. Padwa A, Kassir JM, Xu SL. *J Org Chem* 1997;62:1642.
18. Grimmett, MR. *Science of Synthesis*. Neier, R., editor. Vol. 12. Thieme; New York: 2002. p. 325
Synthesis of imidazoles review



Scheme 1.

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

Table 1



entry	catalyst	solvent	t, °C	time	yield, % ^a
1	Rh ₂ (OAc) ₄	CHCl ₃	140	15 min	51
2	Rh ₂ (CF ₃ COO) ₄	CHCl ₃	140	15 min	0 ^b
3	Rh ₂ (C ₃ F ₇ COO) 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 ₂ Cl ₂	160	15 min	0 ^c
8	Rh ₂ (Oct) ₄	CH ₂ Cl ₂	140	15 min	77
9	Rh ₂ (Oct) ₄	CH ₂ Cl ₂	120	30 min	70
10	Rh ₂ (Oct) ₄	CH ₂ Cl 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

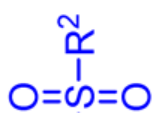
^dbesides starting material, (Z)-2-phenyl-4-tosyl-5,6,7,8-tetrahydro-4H-1,4-oxazocine observed.¹¹

NIH-PA Author Manuscript

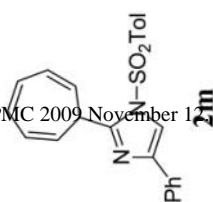
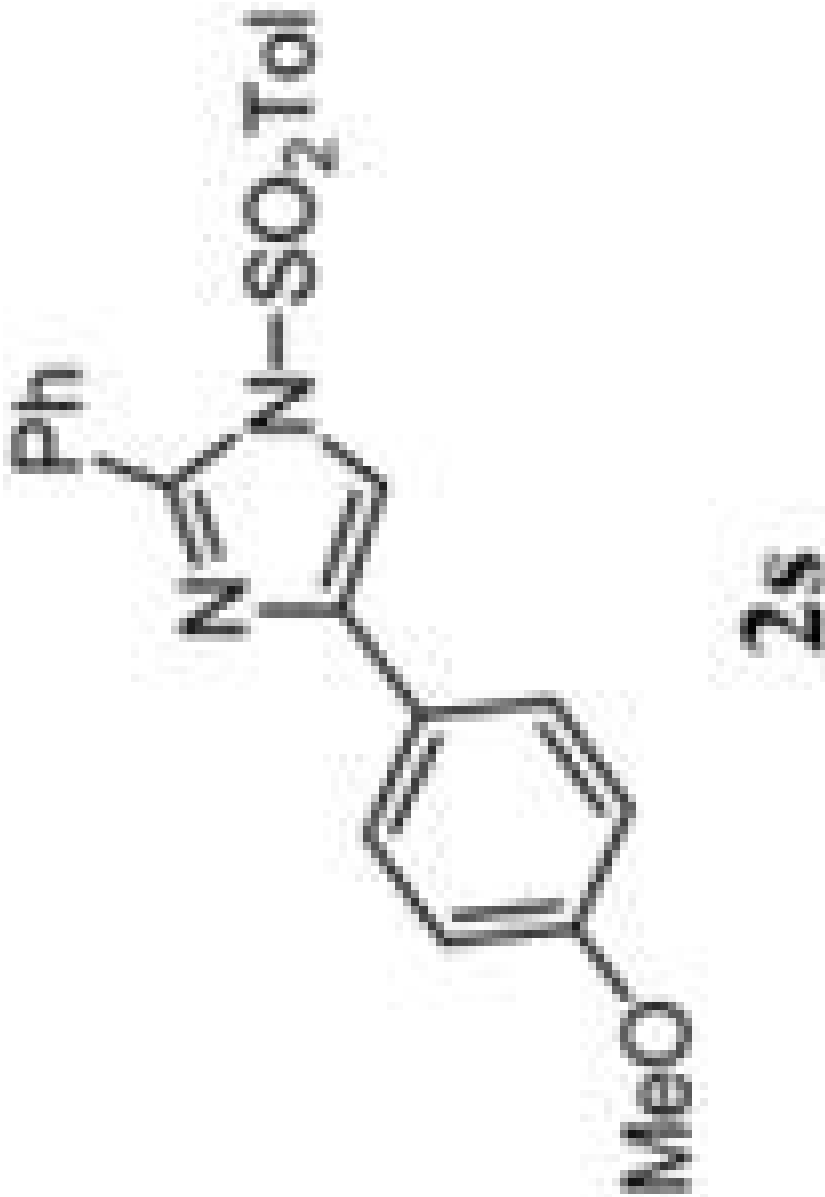
NIH-PA Author Manuscript

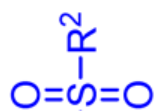
Table 2

NIH-PA Author Manuscript

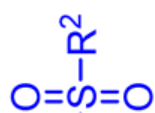


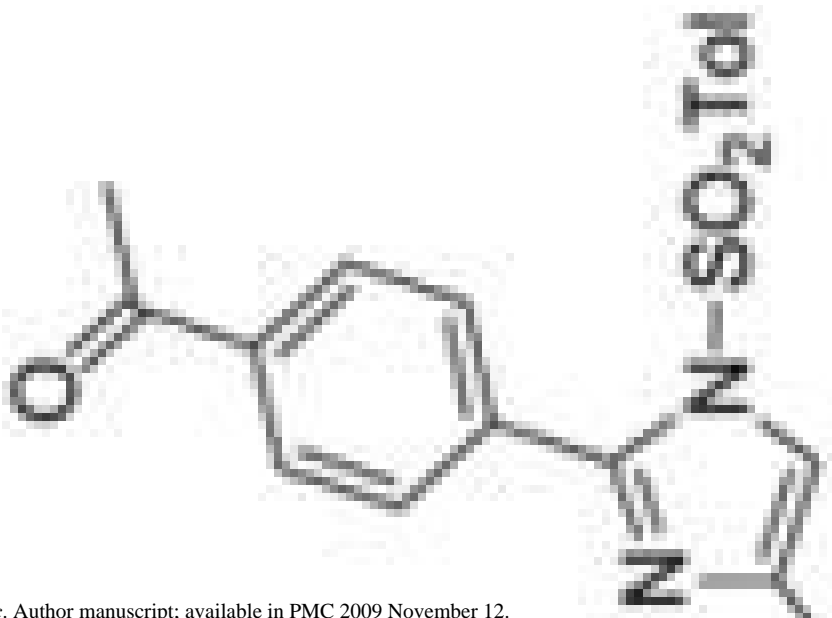
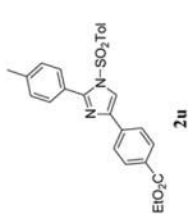
J Am Chem Soc. Author manuscript; available in PMC 2009 November 12

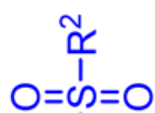
product	yield, % ^a	entry	product	yield, % ^a
 21m	67 ^b	19	 25	64 ^c



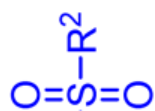
product	yield, % ^a	entry	product	yield, % ^a
 2a	99 ^c	20	 2t	88 ^b

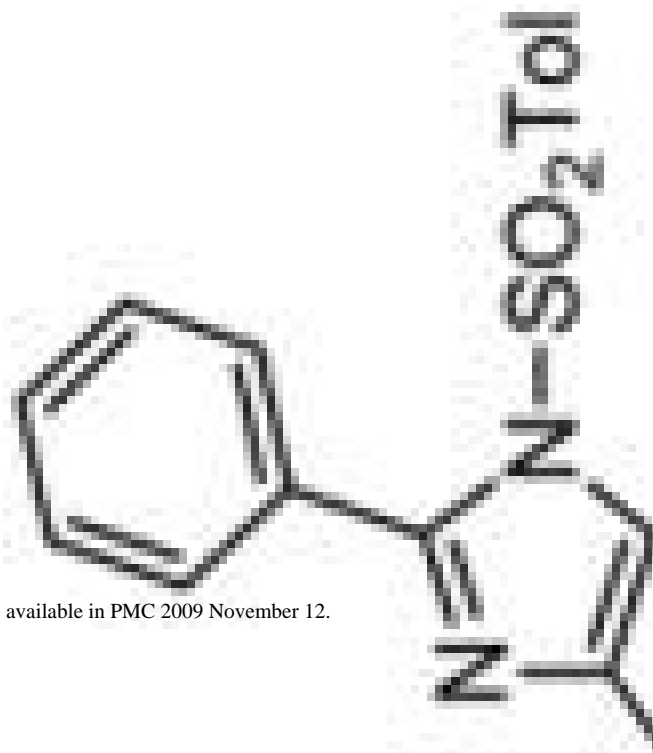
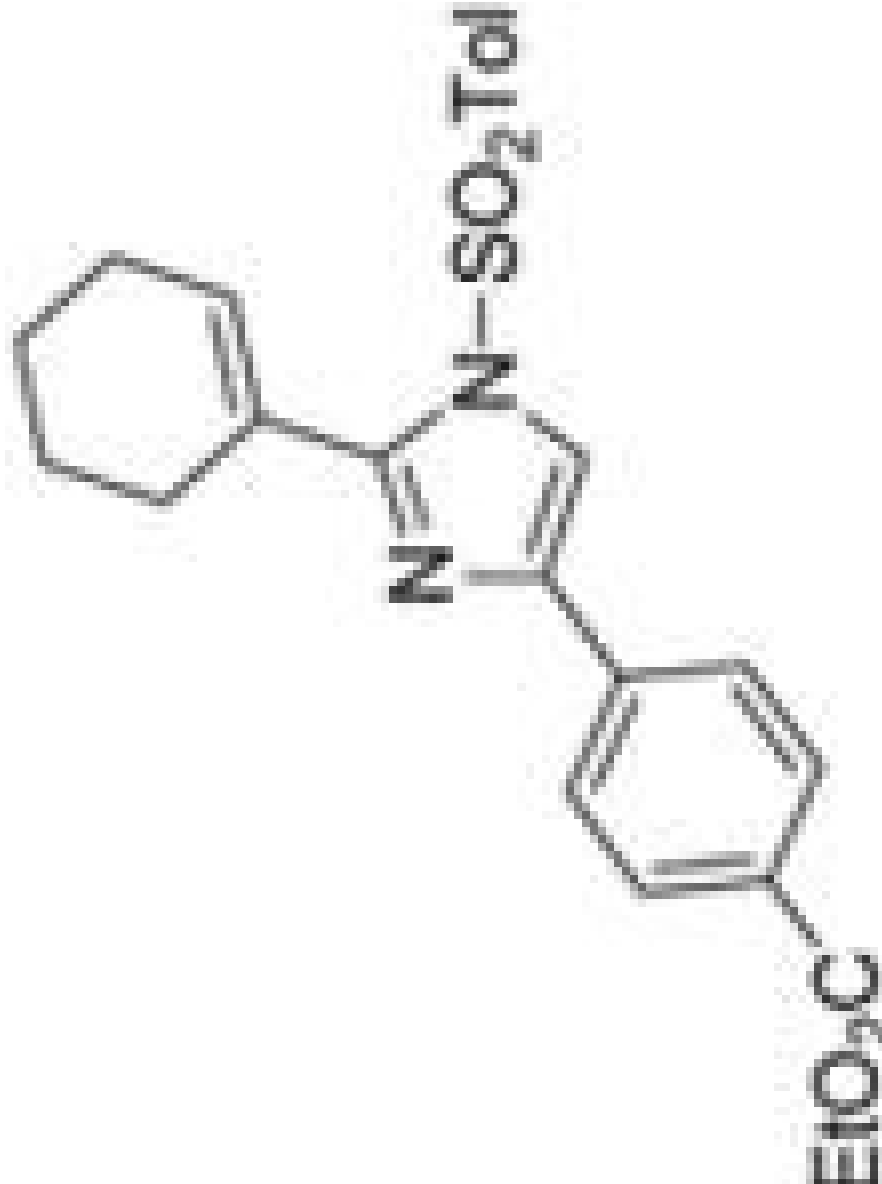


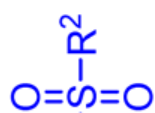
product	yield, % ^a	entry	product	yield, % ^a
	51 ^c	21		88 ^c

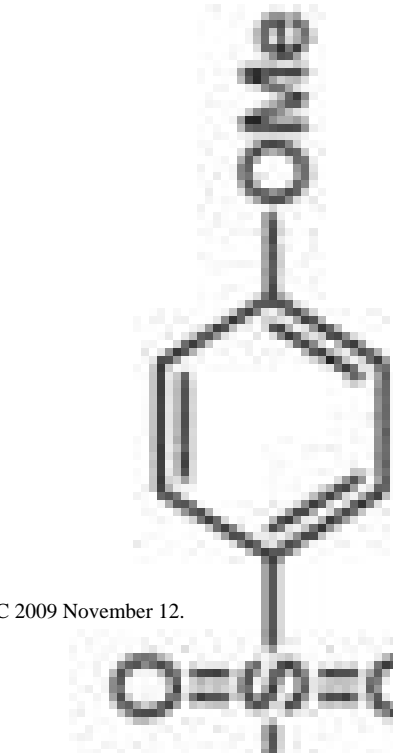
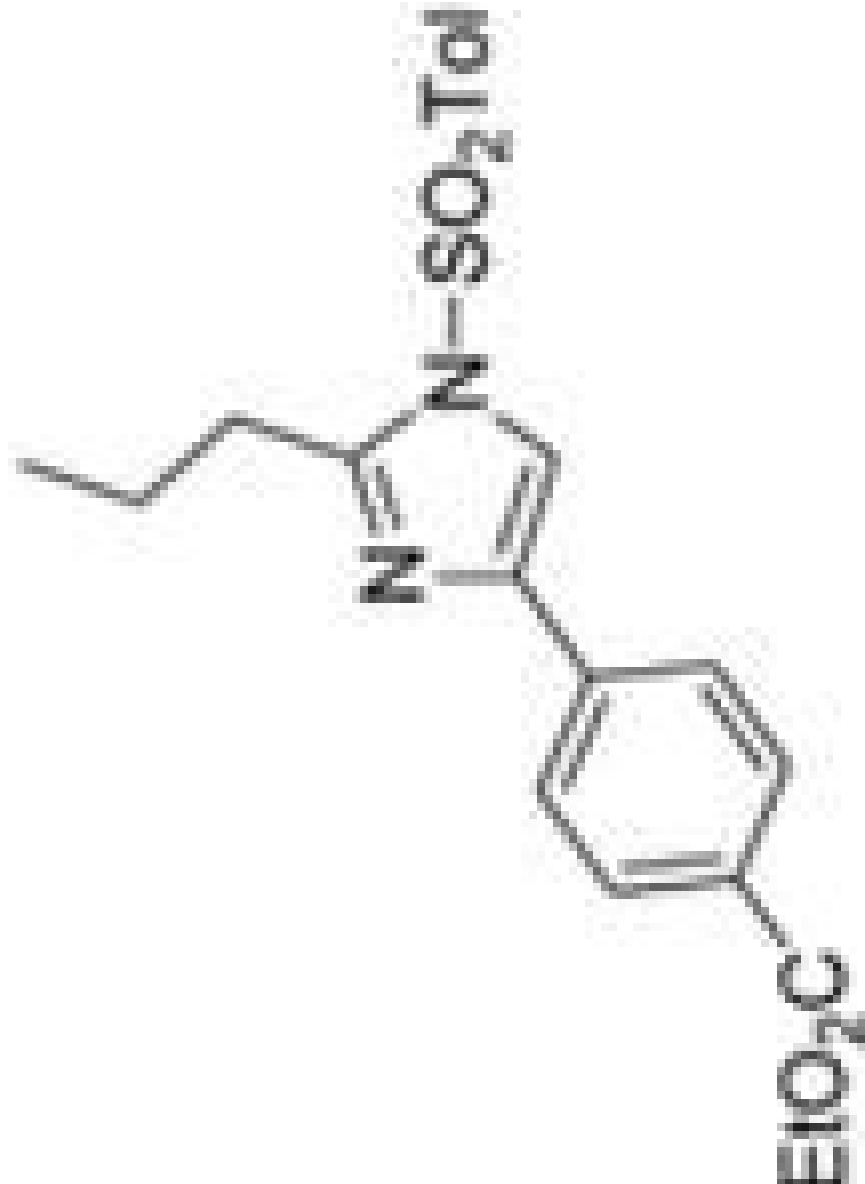


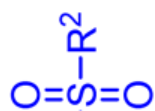
product	yield, % ^a	entry	product	yield, % ^a
---------	-----------------------	-------	---------	-----------------------

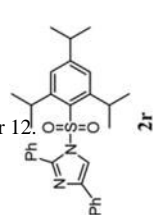
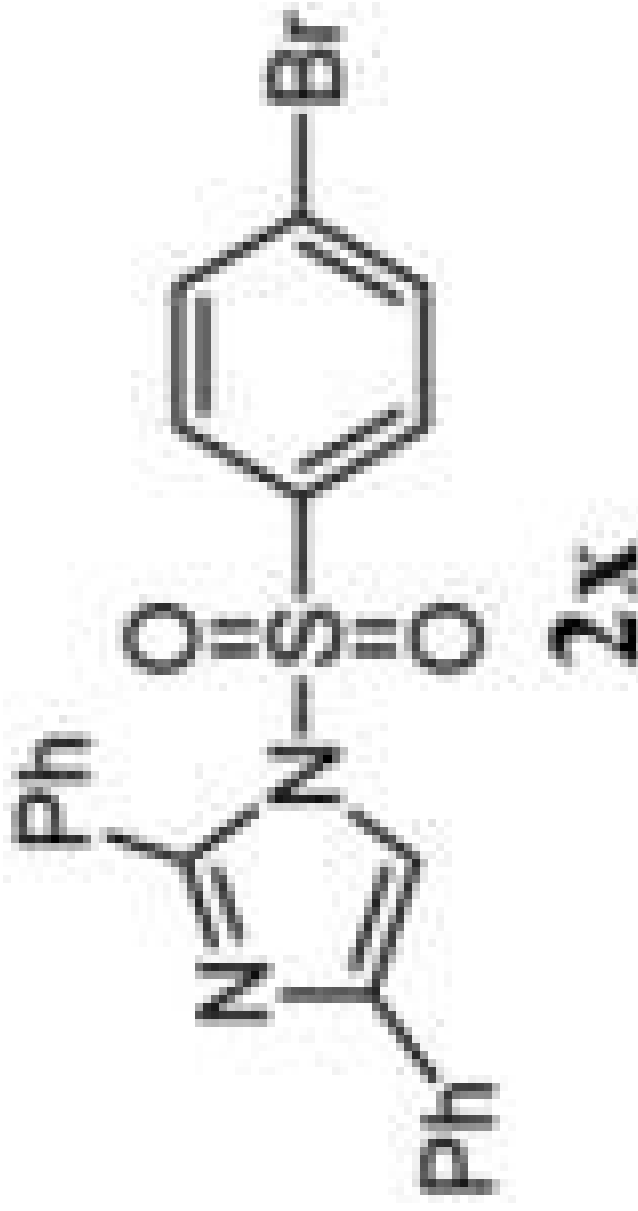


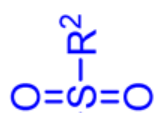
product	yield, % ^a	entry	product	yield, % ^a
	42 ^b	22		74 ^c



product	yield, % ^a	entry	product	yield, % ^a
	76 ^b	23		83 ^c



product	yield, % ^a	entry	product	yield, % ^a
				
	65 ^b	24		72 ^b



product	yield, % ^a	entry	product	yield, % ^a
---------	-----------------------	-------	---------	-----------------------