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PII: S0040-4039(19)30013-9
DOI: https://doi.org/10.1016/j.tetlet.2019.01.012
Reference: TETL 50545

To appear in: *Tetrahedron Letters*

Received Date: 21 November 2018
Revised Date: 4 January 2019
Accepted Date: 8 January 2019

Please cite this article as: Furukawa, A., Hata, T., Shigeta, M., Urabe, H., Rh-catalyzed Intramolecular Cyclization of 1-Sulfonyl-1,2,3-triazole and Sulfinate. Concise Preparation of Sulfonylated Unsaturated Piperidines, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.01.012

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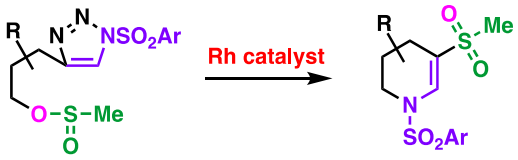

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Rh-catalyzed Intramolecular Cyclization of 1-Sulfonyl-1,2,3-triazole and Sulfinate. Concise Preparation of Sulfonylated Unsaturated Piperidines

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

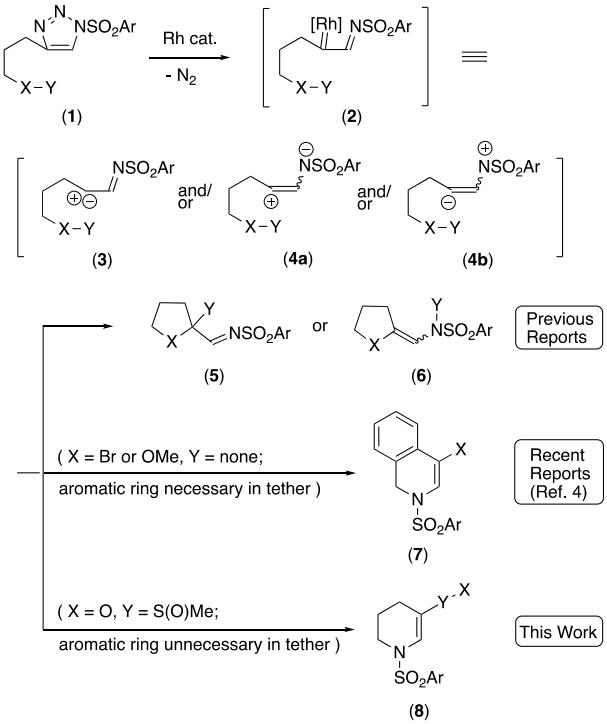
Keywords:
Rhodium
Triazole
Cyclization
Sulfinate
Piperidine

ABSTRACT

When 4-[3-(methanesulfinyloxy)propyl]-1-(arenesulfonyl)-1,2,3-triazoles were treated with rhodium catalysts of the type $Rh_2(RCO_2)_4$, a new intramolecular cyclization took place to afford 2,3-didehydro-1-(arenesulfonyl)-3-(methanesulfonyl)piperidines in good yields. This reaction most likely proceeds via a new reorganization of bonds in the same molecule, consisting of the addition of the sulfur atom of sulfinate ester to the α-(sulfonylimino)carbene moiety generated from the sulfonyltriazole, followed by the counter attack of the sulfonylimino nitrogen to the carbon bearing the oxygen terminus of sulfinate ester.

The rhodium-catalyzed decomposition of 1-sulfonyl-1,2,3-triazoles, generating versatile equivalents of α-(sulfonylimino)carbene or a zwitterionic C-C-N bond linkage, has found widespread use in organic synthesis [1-3]. Its application to intramolecular reactions has provided useful methods for the preparation of various cyclic compounds. Scheme 1 illustrates such a transformation, where the aforementioned reactive intermediate **2** and hence **3**-**4** generated from **1** insert the X-Y bond at the suitable position to give cyclic product **5** [2] or **6** [3]. While numerous important reactions of these types have been reported, a new cyclization of **1** giving **7**, provided that X is a heteroatom group and Y is not present, was recently reported [4]. A more general case where both X and Y are imparted, for example, **1** → **8** in Scheme 1 should be an advanced observation, which is disclosed in this report.

During the course of our study on the rhodium-catalyzed intramolecular cyclization via C-H bond activation [5,6], we were interested in cleaving other heteroatom bonds. When sulfinate ester **9** [7] was treated with the Rh catalyst under the same reaction conditions as those of the previous C-H bond activation (Scheme 2) [6], the expected O-S bond scission was observed as evidenced by the formation of dihydrofuran **11**, obviously produced by the *syn*-elimination of primarily formed sulfoxide **10** [8], albeit in a very low yield. Besides this product corresponding to **5** in Scheme 1 [X-Y = O-S(O)Me], unexpected product **12**, the structure of which was assigned as depicted by spectroscopic means and later confirmed by derivatization to a known compound, was also isolated. As the product **12** is of a unique structure like **8** in Scheme 1 and was obtained still in a moderate yield, we decided to investigate this reaction in more depth.



Scheme 1. Reaction Patterns of Rh-catalyzed Decomposition of Sulfonyltriazole **1**.

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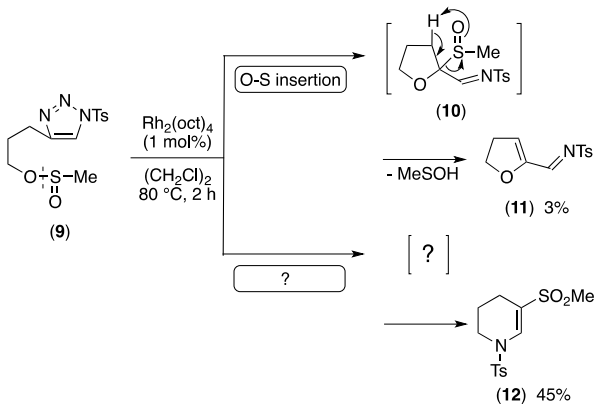
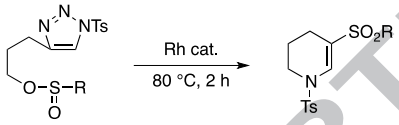


Scheme 2. Rh-catalyzed Reaction of Sulfonyltriazole **9**.[a]
[a] $Rh_2(oct)_4$ refers to $Rh_2(C_7H_{15}CO_2)_4$.

Table 1 shows optimization of the yield of **12**. First, three substrates **9**, **13**, and **15** having different sulfinyl groups were allowed to react with $Rh_2(oct)_4$ (entries 1-3). Among these, methanesulfinate **9** proved the most suitable starting material (entry 1), and other aromatic and sterically more demanding aliphatic sulfinates (**13** and **15**) were found far less useful. Although solvents did not give rise to much difference on the product yields (entries 1 and 4-6), dichloroethane was selected for this reaction (entry 1), because of the highest yield and the least formation of side products. As far as the Rh catalysts and their loads are concerned (entries 1 and 7-12), $Rh_2(OAd)_4$ (2 mol%) was found the catalyst of choice (entry 10) among the several Rh complexes with less or more sterically hindered ligands.

Table 1. Optimization of Substrates, Catalysts, and Conditions.

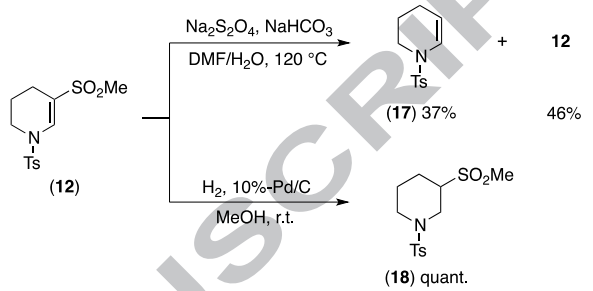


(**9**),(**13**),(**15**) (**12**),(**14**),(**16**)

Entry	R in **9**,**13**,**15**	Rh Cat.[a] (mol%)	Solvent	Yield (%)[b] Product		Recovery	
1	Me (**9**)	$Rh_2(oct)_4$ (1)	$(CH_2Cl)_2$	**12**	(45)[c]	**9**	10
2	*p*-MeC_6H_4- (**13**)	$Rh_2(oct)_4$ (1)	$(CH_2Cl)_2$	**14**	9[d]	**13**	0
3	*t*-Bu (**15**)	$Rh_2(oct)_4$ (1)	$(CH_2Cl)_2$	**16**	0	**15**	39
4	Me (**9**)	$Rh_2(oct)_4$ (1)	PhCl	**12**	53[e]	**9**	0
5	Me (**9**)	$Rh_2(oct)_4$ (1)	1,4-dioxane	**12**	34	**9**	18
6	Me (**9**)	$Rh_2(oct)_4$ (1)	toluene	**12**	37	**9**	0
7	Me (**9**)	$Rh_2(OAc)_4$ (2)	$(CH_2Cl)_2$	**12**	53	**9**	0
8	Me (**9**)	$Rh_2(oct)_4$ (2)	$(CH_2Cl)_2$	**12**	47	**9**	0
9	Me (**9**)	$Rh_2(OPiv)_4$ (2)	$(CH_2Cl)_2$	**12**	42	**9**	0
10	Me (**9**)	$Rh_2(OAd)_4$ (2)	$(CH_2Cl)_2$	**12**	(76)	**9**	0
11	Me (**9**)	$Rh_2(tpa)_4$ (2)	$(CH_2Cl)_2$	**12**	10	**9**	--[f]
12	Me (**9**)	$Rh_2(esp)_2$ (2)	$(CH_2Cl)_2$	**12**	27	**9**	0

[a] oct = $C_7H_{15}CO_2$-, Ac = CH_3CO-, Piv = *t*-BuCO-, OAd = adamantanecarboxylate, tpa = Ph_3CCO_2-, esp = *m*-$C_6H_4(CH_2CMe_2CO_2\text{-})_2$.
[b] Determined by ^1H NMR analysis with internal standard. Isolated yields in parentheses.
[c] Another product **11** was detected as shown in Scheme 2.
[d] Product **11** was also detected in 26% yield.
[e] Impure product with some unknown by-products.
[f] Not determined.

As the formation of **12** was not expected at the outset, its structural confirmation was undertaken by derivatization as shown in Scheme 3. When the known desulfonylation of vinyl sulfones with $Na_2S_2O_4$ [9] was applied to **12**, it was slowly converted to known unsaturated piperidine **17** [10], yet the completion of the reaction was not attempted. Alternatively, standard Pd-catalyzed hydrogenation of **12** gave unsymmetrically disulfonylated piperidine **18**, consistent with the original structure of **12**.



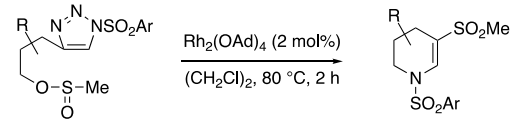
Scheme 3. Structural Confirmation of **12**.

Table 2 summarizes other products obtained by this method. A variety of 1-sulfonyl-1,2,3-triazoles **9** and **19**-**23** gave the desired products **12** and **30**-**34** in good yields (entries 1-6). Starting materials **24**-**27** having substituent β to triazole (or sulfinate ester) also participated in this transformation to afford 5-substituted-2,3-didehydropiperidines **35**-**38** (entries 7-10). However, **28** with a substituent at the α-position to triazole furnished **39** in somewhat lower yield due to the concomitant formation of a small amount of dihydrofuran **41** resulting from the O-S bond insertion (entry 11 and its footnote). In addition to these piperidines, an aromatic substrate **29** can be utilized as well to give dihydroisoquinoline **40** (entry 12). The formation of these substituted piperidine and isoquinoline derivatives shows synthetic flexibility of this method [11].

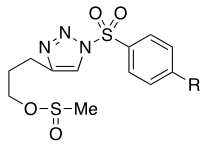
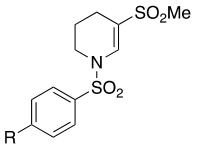
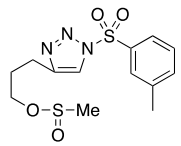
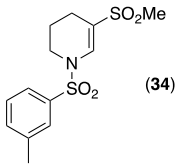
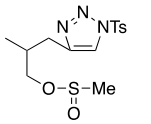
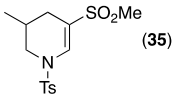
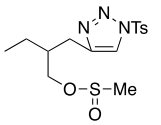
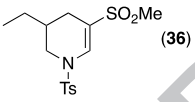
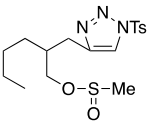
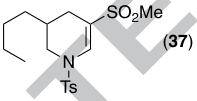
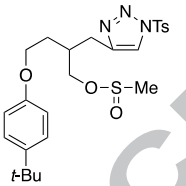
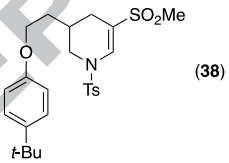
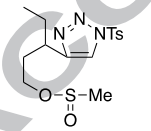
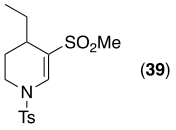
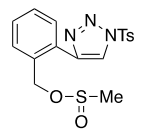
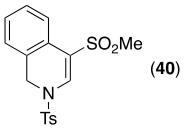
Mechanism of this reaction is proposed as in Scheme 4. The sulfur atom of sulfinate **9** first interacts with the intermediate carbene species like **42a**, forming zwitterion **43a** or **43b** [4], which then collapses to **12** via the intramolecular alkylation of the nitrogen with the sulfinate (path a). Alternatively, alkylation of the sulfonimide with sulfinate takes place first (**42b** → **44**), followed by the addition of the released sulfinate anion to the carbenionic site in **45** to reach **12** (path b).

To get an insight into the above mechanism, a couple of additional experiments were performed. First, the reaction of **9** (entry 1, Table 2) was attempted in the presence of externally added $EtSO_2Na$ as shown in eq 1. Expected products **12** and **46** coming from the uptake of ethanesulfonyl group were not detected, while the starting material was consumed. Thus, the presence of the sulfinate anion is not beneficial to the reaction itself, so that the adoption of path b is discouraged. Secondly, *sec*-alkyl sulfinate **47** was submitted to the reaction (eq 2), giving only an intractable mixture of products including neither desired **48** nor simple insertion product **49**. This suggests that intermediate **43b** of more S_N1-like character than **43a** in path a less contributes to the reaction course [4]. As a whole, the high nucleophilicity of sulfur (**42a**), the formation of by-products **11** and **41** showing that the reaction could take place near the sulfur, and the highly regioselective reaction owing to the totally intramolecular process (**43**) should support that path a is more likely than path b.

Table 2. Preparation of Various Sulfonylated Unsaturated Piperidines.

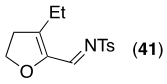


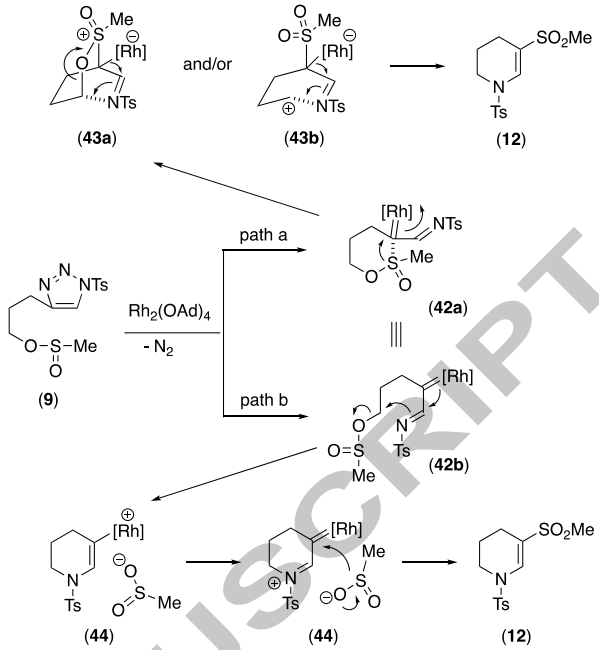
(**9**),(**19**)-(**29**) (**12**),(**30**)-(**40**)

Entry	Substrate		Product		Isolated Yield (%)
1		R = Me (**9**)		(**12**)	76
2		Et (**19**)		(**30**)	76
3		*i*-Pr (**20**)		(**31**)	73
4		OMe (**21**)		(**32**)	59
5		Br (**22**)		(**33**)	51
6		(**23**)		(**34**)	56
7		(**24**)		(**35**)	58
8		(**25**)		(**36**)	61
9		(**26**)		(**37**)	50
10		(**27**)		(**38**)	76
11		(**28**)		(**39**)	43[a]
12		(**29**)		(**40**)	52[b]

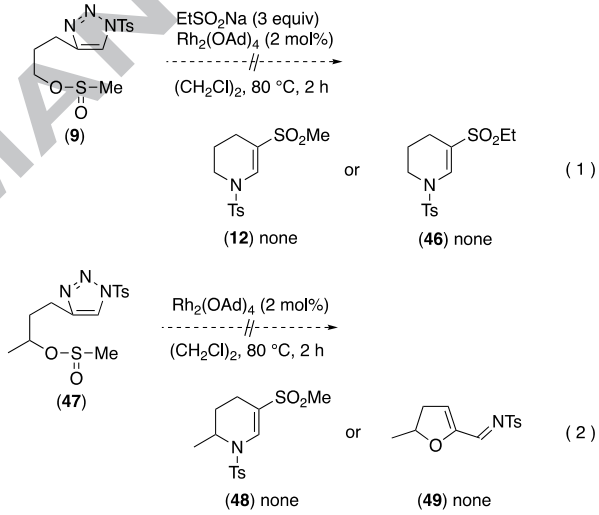
[a] By-product **41** (18%, see below), like **11** in Scheme 2, was also detected.

[b] This reaction was performed with 8 mol% of $Rh_2(OAd)_4$.

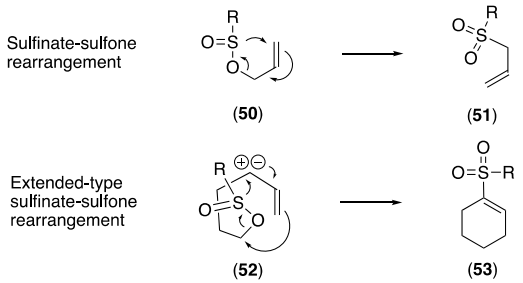




Scheme 4. Proposed Reaction Mechanism.



It is worth noting that this reaction at least formally represents a new version of sulfinate-sulfone rearrangement as shown in Scheme 5. While the usual sulfinate-sulfone rearrangement is performed on the allylic system from **50** to **51**, providing a versatile method for the preparation of allyl sulfones **51** [7], the present reaction incorporates the carbenoid and sulfinate carbons to the above system to effect the formation of cyclic sulfones **53** from **52** in good yields.



Scheme 5. New Variant of Sulfinate-sulfone Rearrangement.

In summary, the treatment of 1-sulfonyl-1,2,3-triazoles having a side chain of sulfinyl ester with a catalytic amount of $Rh_2(OAd)_4$ afforded a variety of *C*,*N*-disulfonylated unsaturated piperidines, which should be versatile synthetic intermediates

[12] based on their vinyl sulfone [7] and enamide [13] moieties. From the mechanistic point of view, the new bond reorganization between sulfonyltriazole and sulfinate should be quite interesting, demonstrating a unique collaboration of the modern Rh-catalyzed reactions and traditional organosulfur chemistry.

Acknowledgments

This research was supported partially by JSPS KAKENHI Grant Numbers JP26810019 and 25288018 and JST PRESTO Grant Number JPMJPR14KC.

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Supplementary Material

Experimental procedures and spectral data (PDF)

• Strictly ordered scission and formation of a few bonds are attained in one flask

• Traditional S and new Rh chemistries elegantly collaborated to yield a new field

• Sulfur magic between its two exchangeable states leads an intriguing bond behavior

• Versatile unsaturated piperidines with N-sulfonyl protection are readily accessible