A one-pot construction of acridones by rhodium catalyzed reaction of N-phenyl-2-(1-sulfonyl-1*H*-1,2,3-triazol-4-yl)aniline

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Graphical Abstract

A one-pot construction of acridones by rhodium catalyzed reaction of N-phenyl-2-(1-sulfonyl-1H-1,2,3-triazol-4-yl)aniline

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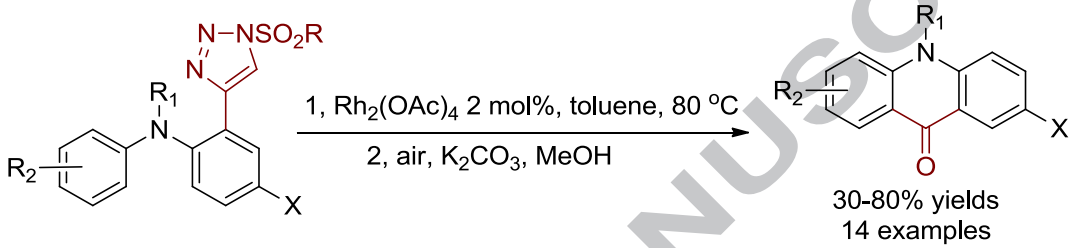

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A one-pot construction of acridones by rhodium catalyzed reaction of N-phenyl-2-(1-sulfonyl-1*H*-1,2,3-triazol-4-yl)aniline

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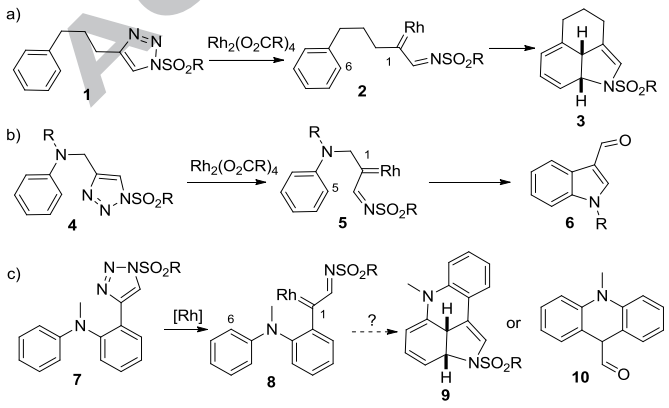
ABSTRACT

Abstract: A one-pot synthesis of N-alkyl acridone via rhodium catalyzed decomposition of N-phenyl-2-(1-sulfonyl-1*H*-1,2,3-triazol-4-yl)aniline and subsequent oxidative C-C bond fragmentation has been developed. 14 examples are presented and the yields range from 30% to 80%.

Since demonstrated as a viable metal carbene precursor in 2008,[1] N-sulfonyl 1,2,3-trizaole has attracted intensive attention in this respect.[2-20] Comparing with probably the most studied carbene progenitor diazo compounds in organic synthesis, N-sulfonyl 1,2,3-trizaoles feature some advantages. First, not as the hazardous and dangerous diazo compounds, triazoles are relatively more stable and safer for routine handling in laboratory. Second, it is convenient to prepare N-sulfonyl 1,2,3-trizaoles from corresponding terminal alkynes in almost neutral conditions which would facilitate the studies of carbene chemistry in complex molecule settings. And more, the unique aza-vinyl metal carbenes generated from triazole compounds exhibit more diverse reactivities because of potential participation of α-imino group in reactions.

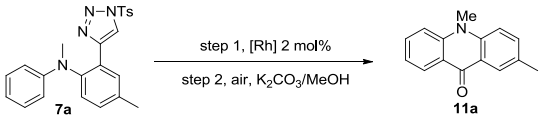


Scheme 1. a) Tricycles synthesis from sulfonyl triazoles; b) indolyl aldehyde synthesis from sulfonyl triazoles; c) question current research aims to answer.

Miura and Murakami group have discovered that triazole-derived aza-vinyl rhodium carbenes **2** react with aromatic ring at 6-position leading to tricyclic N-heterocycles **3**.[21] Our laboratory and Lin's laboratory discovered that aza-vinyl rhodium carbenes **5** derived from triazoles **4** cyclize onto anilinyl ring at 5-position to give bicyclic N-heterocyclic aldehyde **6** upon losing sulfonyl amine.[22,23] Bearing these findings in mind, we are curious what is the behavior of analogous α-imino carbene **8**, which also has an aromatic π-bond at 6-position; in other words, the reaction of triazole **7** will give teracycle **9** as the formation of **3** from **1** or aldehyde **10** following the process of the conversion of triazole **4** to indolyl aldehyde **6**. Here we would like to communicate our findings.

Our study started with triazole **7a**. In the presence of catalytic amount of rhodium acetate, a solution of **7a** in toluene was heated to 60 °C under nitrogen for 2 hours, and then the reaction mixture was treated with K_2CO_3 in methanol under air at room temperature overnight. To our surprise, acridone **11a** was obtained in 42% isolated yield (Table 1 entry 2). When the reaction temperature was raised to 80 °C, the yield increased to 62% (entry 3); whereas enhancement of the temperature to 100 °C didn't result in further improvement in yield (entry 5). On the other hand, the sulfonyl triazole starting material can keep intact in 40 °C for several hours (entry 1). Replacement of $Rh_2(OAc)_4$ with $Rh_2(esp)_2$ as catalyst resulted in a reduced yield to 50% (entry 6). When the first step was also carried out in air, **11a** was obtained in only 43% yield suggesting that the air might act adversely in the first step reaction (entry 7). Other non-nucleophilic solvents such as dichloroethane and chloroform are also feasible for this reaction though giving lower yields (entries 8 and 9). This reaction could proceed smoothly at a 5 mmol scale showing the potential for its large scale application (entry 4).

Table 1, Condition optimization for one-pot synthesis of N-methyl acridone[a]

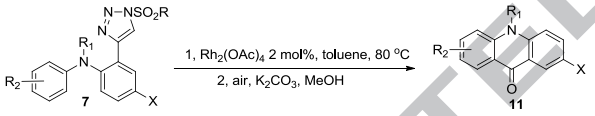


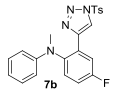
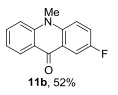
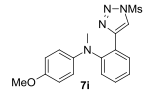
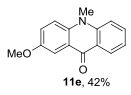
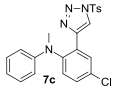
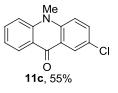
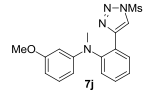
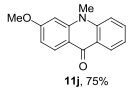
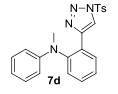
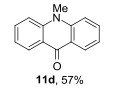
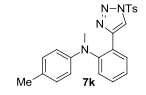
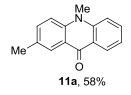
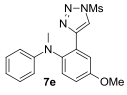
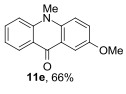
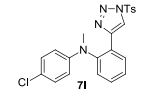
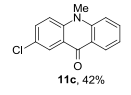
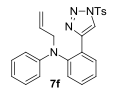
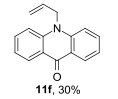
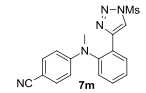
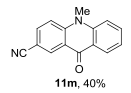
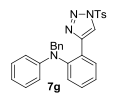
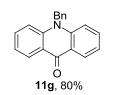
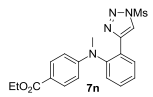
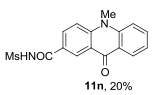
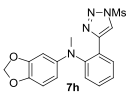
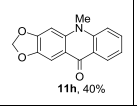
Entry	Conditions for first step			atmosphere		Yield[b]
	[Rh](2 mol%)	Solvent	T /°C	Step 1	Step 2	
1	$Rh_2(OAc)_4$	toluene	40	N_2	air	–
2	$Rh_2(OAc)_4$	toluene	60	N_2	air	42%
3	$Rh_2(OAc)_4$	toluene	80	N_2	air	62%
4	$Rh_2(OAc)_4$	toluene	80	N_2	air	60%[c]
5	$Rh_2(OAc)_4$	toluene	100	N_2	air	60%
6	$Rh_2(esp)_4$	toluene	80	N_2	air	50%
7	$Rh_2(OAc)_4$	toluene	80	air	air	43%
8	$Rh_2(OAc)_4$	DCE	80	N_2	air	51%
9	$Rh_2(OAc)_4$	chloroform	80	N_2	air	54%

a, Unless otherwise specified, the reaction was conducted on a 0.1 mmol scale b, isolated yield; c, carried out in a 5 mmol scale.

The acridone framework exists widely in nature and has versatile biological activities.[24-26] However there are limited strategies that could access this class of tricyclic alkaloids.[27] The most common method applies Friedel-Crafts reaction to construct the middle ring.[28-30] Recently, direct oxidative C-H amination was used to build the middle ring.[31] A pretty unique approach that completes the tricyclic system through a final 6 π - electrocyclization to make the side ring has also emerged.[32] The current transformation of **7a** to **11a** provides a new approach to acridone framework. Accordingly, more substrates were made and subjected to the optimal conditions to prove the generality of this method. The results are listed in Table 2.

Table 2. One-pot synthesis of acridone derivatives[a]

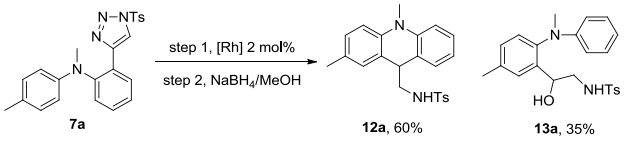


entry	substrate	product, yield[b]	entry	substrate	product, yield[b]
1		 11b, 52%	8		 11e, 42%
2		 11c, 55%	9		 11j, 75%
3		 11d, 57%	10		 11a, 58%
4		 11e, 66%	11		 11c, 42%
5		 11f, 30%	12		 11m, 40%
6		 11g, 80%	13		 11n, 20%
7		 11h, 40%			

a, reactions were conducted on a 0.1 mmol scale; b isolated yields.

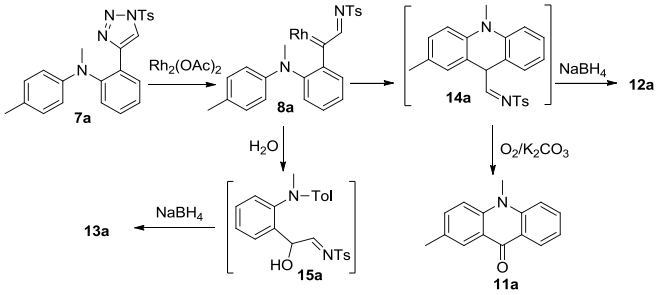
Acridones **11b-11e** were obtained from corresponding ortho-aminophenyltriazoles **7b-7e** in yields increasing from 52% for electro-deficiently fluorinated **7b** to 66% for electro-rich methoxylated **11e**, demonstrating that electro-donating group on the aromatic ring of the triazole component would facilitate acridone formation. The relatively low yield of **11f** probably reflects the interference by the nearby alkene group that would compete for metal carbene. Very interestingly, replacement of the N-methyl group with N-benzyl group resulted in a dramatically enhancement of product yield to 80%, presumably due to the greater steric repulsion caused by the bigger Bn vs Me, which would push the bulky Rhodium carbene toward the reacting aniline ring. While the reason accounting for the unexpected low yield of **11h** from **7h** was not clear at present stage, the more than 30% divergence in yields between **11i** and **11j** might reflect the different nucleophilicity of the aromatic carbon defined by the methoxyl substitution in **7i** and **7j** accordingly. It is also worth to note that the reaction of **7j** afforded the para-cyclized product absolutely and no ortho-cyclized acridone was detected. This excellent regioselectivity might be a consequence of the steric repulsion of the meta-methoxyl group toward the bulky rhodium carbene segment. p-Chlorination on the aniline also afford product **11c** in decreased yield, similar to the effect of *p*-cyanation on the yield of **11m**. Thermal decomposition of p-carbonylated phenylamino trizaole **7n** gave rise to acridone **11n**. The low yield obtained probably due to an additional O to N acyl transfer step for the formation of **11n** from **7n**.

To gain more information, the residue of the first step, namely rhodium catalyzed reaction of **7a**, was treated with $NaBH_4$ in methanol. Tosyl amide **12a** was isolated in 60% yield accompanied with 2-hydoxyl tosyl amide **13a** in 35% yield.



Scheme 2. Direct treatment of the residue of first step with $NaBH_4$

These data strongly suggested tosyl imine **14a** as the direct product and **15a** as the side product of the first step. In second step, **14a** is converted to **11a** through oxidative fragmentation in air.[33-35] The side product of **13a** derived from the reaction of carbene intermediate **8a** with water.[36] Reduction of **14a** and **15a** with $NaBH_4$ afford **12a** and **13a** respectively.



Scheme 3. Explanation of the origins for observed products.

In summary, we have demonstrated that *N*-aryl-2-(1-sulfonyl-1*H*-1,2,3-triazol-4-yl)aniline can be converted to acridones smoothly by a one-pot operation. First step operates through a rhodium catalyzed decomposition of sulfonyl triazoles to corresponding rhodium carbene which cyclized with the other N-aryl group to form Acridanyl sulfonylimine. Subsequent oxidation with air affords related acridones in useful yields.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2015.xx

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